

**DR. REDDY'S LABORATORIES (PTY) LTD.
APPROVED PROFESSIONAL INFORMATION
CIFLOC 250/500/750 (TABLETS)**

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIFLOC 250

CIFLOC 500

CIFLOC 750

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIFLOC 250: Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin.

CIFLOC 500: Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin.

CIFLOC 750: Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin.

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Film-coated tablet.

CIFLOC 250: White, oval shaped film-coated tablets debossed with 'R' on one side and '126' on other side.

CIFLOC 500: White, oval shaped, bevelled edge film-coated tablets debossed with 'R' on one side and '127' on other side.

CIFLOC 750: White, modified capsule shaped film-coated tablets debossed with 'R' on one side and '128' on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CIFLOC 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.

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CIFLOC 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.

CIFLOC 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 influenzae* 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*.

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* and *Streptococcus pyogenes*.

Severe and/or complicated gastro-intestinal Infections: Infective diarrhoea caused by *E. coli*, *Campylobacter jejuni*, *Shigella flexneri* and *Shigella sonnei*.

Severe and/or complicated bone Infections: Osteomyelitis due to susceptible Gram-negative 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 CIFLOC. Therapy with CIFLOC 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 - 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.

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.

If the patient is unable to take CIFLOC tablets because of the severity of their illness or for other reasons, therapy should be commenced with intravenous ciprofloxacin. After intravenous administration the treatment can be continued orally.

Special populations

Impaired renal or liver function

In patients with reduced renal function, the half-life of ciprofloxacin is prolonged and the dose needs to be adjusted.

For patients with changing renal function or patients with renal impairment and hepatic insufficiency, monitoring of drug serum levels provide the most reliable basis for dose adjustment.

Dose adjustment of CIFLOC for patients with kidney and/or liver insufficiency:	
1. Kidney insufficiency:	
• $CL_{cr} \geq 31$ ml/min/1,73 m ²	Max 800 mg/day intravenously
• $CL_{cr} \leq 30$ ml/min/1,73 m ²	Max 400 mg/day intravenously
• Impaired renal function and	Max 400 mg/day on days after dialysis.

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haemodialysis	
2. Impaired renal function and CAPD (chronic ambulatory peritoneal dialysis):	
<ul style="list-style-type: none"> • Oral administration of either CIFLOC 500 mg tablet or CIFLOC 2 x 250 mg tablets is indicated. • For CAPD patients with peritonitis, the recommended daily oral dose is 500 mg 4 times daily. 	
3. Liver function disturbances	No dose adjustments.
4. Liver and kidney insufficiency	As in point 1 above.

Elderly

Elderly patients should receive a dose as low as possible. This will depend on the severity of the illness and on the creatinine clearance.

Method of administration

CIFLOC tablets should be swallowed whole with plenty of liquid and may be taken with or without meals.

If taken on an empty stomach, CIFLOC is absorbed more rapidly.

CIFLOC should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 CONTRAINDICATIONS

Children under 18 years and in growing adolescents. Experimental evidence indicates that species variable reversible lesions of the cartilage of weight-bearing joints has been seen in immature members of certain animal species.

- Pregnancy and lactation.
- Patients who have shown hypersensitivity to ciprofloxacin or any other quinolones, or to any of the inactive ingredients in the formulation (see-section 2).
- Concomitant administration of CIFLOC and tizanidine (see section 4.5).
- Concomitant use of ciprofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to prolonged QTcF interval known to be associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with

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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.
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers in patients with moderate to severe renal impairment and in the elderly.
- Use of fluoroquinolones is contraindicated in patients with confirmed mitral valve and /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

Central Nervous System

In epileptics and in patients who have suffered from previous CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), CIFLOC 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).

In some instances, the CNS reactions occurred already after the first administration of CIFLOC.

Depression or psychosis can progress to self-endangering behaviour. In these cases, CIFLOC has to be discontinued (see sections 4.3 and 4.8).

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving CIFLOC. CIFLOC should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Musculoskeletal System

CIFLOC may exacerbate the symptoms of myasthenia gravis.

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The use of CIFLOC in patients with myasthenia gravis is contraindicated if alternative appropriate antibiotic choices are available (see section 4.3).

Caution is advised as fluoroquinolones, including CIFLOC, are associated with an increased risk of tendonitis and tendon rupture in all ages (see sections 4.3 and 4.8). This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid medicines, in patients with solid organ (kidney, heart or lung) transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendonitis and tendon rupture have also occurred in patients taking fluoroquinolones, like CIFLOC, who do not have the above risk factors.

Tendonitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with CIFLOC, even within the first 48 hours of treatment.

Inflammation and ruptures of tendon may also occur up to several months after discontinuation of CIFLOC therapy.

At any sign of tendonitis (e.g. painful swelling, inflammation), the administration of CIFLOC should be discontinued and a medical practitioner be consulted. Care should be taken to keep the affected limb at rest.

CIFLOC 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).

Cardiac disorders

There is some evidence of an increased risk of aortic aneurysm and/or dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, fluoroquinolones such as CIFLOC, should only be used in patients at risk after careful benefit-risk assessment and 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.

Therefore, CIFLOC, should only be prescribed to patients with a pre-existing dilated aorta, aortic aneurysm/dissection, or the presence of other risk factors predisposing to aortic aneurysm/dissection, where other antimicrobials have been considered not to be an appropriate treatment option, have failed, are contraindicated or cannot be tolerated.

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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.

CIFLOC has been associated with QT prolongation (see sections 4.3 and 4.8).

Concomitant use of CIFLOC 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, although inconclusive, of a possible association between oral 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).

Renal or hepatic impairment

Care is necessary in patients with impaired renal or hepatic function.

Alteration of the dosage regimen is necessary for patients with impairment of renal function or with impairment of both renal and hepatic function (see section 4.2).

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.

Influence on laboratory parameters / urinary sediment

Temporary increases 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, crystalluria or haematuria have been reported.

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

CIFLOC monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections CIFLOC must be co-administered with other appropriate antibacterial agents.

Children and adolescents

CIFLOC is contraindicated in children less than 18 years. In children arthropathy is reported to occur commonly. The use of CIFLOC should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with CIFLOC should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Prolonged, disabling and potentially irreversible serious adverse drug reactions

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

Streptococcal infections (including *Streptococcus pneumoniae*)

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

Intra-abdominal infections

There are limited data on the efficacy of CIFLOC in the treatment of post-surgical intra-abdominal infections.

Infections of the bones and joints

CIFLOC should be used in combination with other antimicrobial agents depending on the microbiological results.

Complicated urinary tract infections and pyelonephritis

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

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reactions occurs, CIFLOC should be discontinued and adequate medical treatment is required.

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Vision disorders

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

Photosensitivity

Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking CIFLOC should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with CIFLOC should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Gastrointestinal System

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, CIFLOC should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Renal and urinary system

Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving CIFLOC should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since CIFLOC is largely excreted unchanged via renal pathway dose adjustment is needed in patients with

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impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). 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.

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. CIFLOC should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance

During or following a course of treatment with CIFLOC, bacteria that demonstrate resistance to CIFLOC 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

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of CIFLOC and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with CIFLOC should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate

The concomitant use of CIFLOC with methotrexate is not recommended (see section 4.5).

Interaction with tests

The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking CIFLOC.

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

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life-threatening or fatal, have been reported with CIFLOC (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, CIFLOC 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 CIFLOC, treatment with CIFLOC must not be restarted in this patient at any time.

Sodium content

CIFLOC 250 contains 0,63 mg sodium per tablet, CIFLOC 500 contains 1,26 mg sodium per tablet and CIFLOC 750 contains 1,89 mg sodium per tablet respectively.

4.5 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

The use of enalapril, an angiotensin converting enzyme (ACE) inhibitor, may lead to renal impairment due to altered renal haemodynamics in particular clinical situations or with other medicines that affect glomerular filtration. Increased serum creatinine and blood urea nitrogen, and more rarely crystalluria and macrohaematuria, have been observed in patients taking CIFLOC.

Concurrent administration of ciprofloxacin and glibenclamide can potentiate the action of glibenclamide, leading to hypoglycaemia.

Effects of other products on ciprofloxacin

Drugs known to prolong QT interval

CIFLOC, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, CIFLOC should be administered either 1 to 2 hours before or at least 4 hours after these preparations. The restriction does not apply

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to antacids belonging to the class of H₂ receptor blockers.

Food and Dairy Products

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

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and CIFLOC increases ciprofloxacin serum concentrations.

Metoclopramide

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

Omeprazole

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

Effects of ciprofloxacin on other medicinal products

Agomelatine

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.

Tizanidine

Tizanidine must not be administered together with CIFLOC (see section 4.3). There was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of CIFLOC, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of CIFLOC and theophylline can cause an undesirable increase in serum theophylline

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concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of CIFLOC and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of CIFLOC and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Cyclosporin

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

Vitamin K antagonists

Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of CIFLOC 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 CIFLOC with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Duloxetine

Concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. A possible interaction with ciprofloxacin can be expected upon concomitant administration (see section 4.4).

Ropinirole

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

Lidocaine

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Concomitant use of lidocaine containing medicinal products with CIFLOC, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22 %. Although lidocaine treatment was well tolerated, a possible interaction with CIFLOC associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg CIFLOC with clozapine for 7 days, serum concentrations of clozapine and N-desmethylozapine were increased by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with CIFLOC are advised (see section 4.4).

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold after an oral dose of 50 mg given concomitantly with 500 mg CIFLOC. Therefore, caution should be used prescribing CIFLOC concomitantly with sildenafil taking into consideration the risks and the benefits.

Zolpidem

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

4.6 PREGNANCY AND LACTATION

Pregnancy

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

Breast-feeding

Mothers taking CIFLOC should not breastfeed their infants.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

CIFLOC may impair the ability to drive or operate machinery, especially when alcohol is also taken.

4.8 UNDESIRABLE EFFECTS

The most frequently reported adverse drug reactions are nausea and diarrhoea.

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System Organ Class	Frequency	Adverse effect
Infections and infestations	Less frequent	Mycotic superinfections
Blood and lymphatic system disorders	Less frequent	Eosinophilia, leucopenia, anaemia, neutropenia, leucocytosis, thrombocytopenia, thrombocytopenia, haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening)
	Frequency unknown	Granulocytopenia, thrombocytosis, altered prothrombin values
Immune system disorders	Less frequent	Allergic reaction, allergic oedema / angioedema, anaphylactic reaction, anaphylactic shock (life-threatening) (see section 4.4), serum sickness like reaction
Endocrine disorders	Frequency unknown	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders	Less frequent	Decreased appetite, hyperglycaemia, hypoglycaemia (see section 4.4)
	Frequency unknown	Hypoglycaemic coma (see section 4.4)
Psychiatric disorders*	Less frequent	Psychomotor hyperactivity / agitation, confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4), hallucinations, psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4), nightmares
	Frequency unknown	Mania, incl. hypomania
Nervous system disorders	Less frequent	Headache, dizziness, sleep disorders, taste disorders, par- and dysaesthesia, hypoaesthesia, tremor, seizures

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		(including status epilepticus see section 4.4), vertigo, migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri, tiredness, nervousness and trembling, insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions
	Frequency unknown	Peripheral neuropathy and polyneuropathy (see section 4.4)
Eye disorders*	Less frequent	Visual disturbances (e.g. diplopia), visual colour distortions
Ear and labyrinth disorders*	Less frequent	Tinnitus, hearing loss / hearing impaired, vertigo
Cardiac disorders**	Less frequent	Tachycardia
	Frequency unknown	Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see sections 4.4 and 4.9)
Vascular disorders**	Less frequent	Vasodilatation, hypotension, syncope, vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea (including asthmatic condition)
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, impaired taste and smell
	Less frequent	Vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence, antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4), pancreatitis
Hepatobiliary disorders	Less frequent	Increase in transaminases, increased bilirubin, hepatic impairment, cholestatic icterus, hepatitis, liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria, photosensitivity reactions (see section 4.4), petechiae, erythema multiforme, erythema nodosum, Stevens - Johnson Syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening)

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	Frequency unknown	Acute generalised exanthematous pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders*	Less frequent	Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia, myalgia, arthritis, increased muscle tone and cramping, muscular weakness, tendinitis, tendon rupture (predominantly Achilles tendon) (see section 4.4), exacerbation of symptoms of myasthenia gravis (see section 4.4)
Renal and urinary disorders	Less frequent	Renal impairment, renal failure, haematuria, crystalluria (see section 4.4), tubulointerstitial nephritis
General disorders and administration site conditions*	Less frequent	Asthenia, fever, oedema, sweating (hyperhidrosis)
Investigations	Less frequent	Increase in blood alkaline phosphatase, increased amylase
	Frequency unknown	International normalized ratio increased (in patients treated with Vitamin K antagonists), hyperglycaemia

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

4.9 OVERDOSE

In the event of overdosage, reversible renal toxicity has been reported. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg - or Ca-containing antacids which reduce the absorption of CIFLOC. Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Fluoroquinolones

ATC code: J01MA02

Ciprofloxacin is a synthetic 4-quinolone derivative and inhibits gyrase-mediated DNA supercoiling, with *in vitro* bactericidal activity against several Gram-negative and Gram-positive organisms.

The following organisms are usually resistant:

Enterococcus faecium, *Ureaplasma urealyticum*, *Nocardia asteroides*.

With a few exceptions, anaerobes are moderately sensitive (e.g. *Peptococcus*, *Peptostreptococcus*) to resistant (e.g. *Bacteroides*, *Treponema pallidum*).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ciprofloxacin is well absorbed and peak serum levels are obtained within 1 - 3 hours after oral dosing. The absolute oral bioavailability is approximately 70 % with no substantial loss by first pass metabolism. Food does not impair oral absorption, but may delay the time to peak serum concentrations.

Distribution

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 the active form in the saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, prostatic secretions, cerebrospinal fluid and the aqueous humor. High concentrations are achieved in bile. Protein binding is low and ranges from 20 to 40 %.

Elimination

Ciprofloxacin is eliminated principally by urinary excretion, but non-renal excretion may account for about a third of elimination and includes hepatic metabolism, biliary excretion and possibly transluminal secretions across the intestinal mucosa.

Elimination occurs primarily by the kidneys and mainly during the first 12 hours after dosing. Excretion is virtually complete after 24 hours; about 40 % to 50 % is excreted in urine as unchanged ciprofloxacin and about 15 % as

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metabolites. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Starch

Film coating:

Hypromellose

Polyethylene glycol 400

Titanium dioxide

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 °C.

Keep the HDPE containers tightly closed.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

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6.5 NATURE AND CONTENTS OF CONTAINER

CIFLOC 250:

50, 100 and 500 tablets packed into white opaque plastic containers.

Clear PVC / white paper backed silver coloured aluminium blister packs consisting of 10 and 100 tablets in strips of 10, packed into a printed carton.

CIFLOC 500:

50, 100 and 500 tablets packed into white opaque plastic containers.

Clear PVC / white paper backed silver coloured aluminium blister packs consisting of 10 and 100 tablets in strips of 10, packed into a printed carton.

CIFLOC 750:

50, 100 and 500 tablets packed into white opaque plastic containers.

Clear PVC / white paper backed silver coloured aluminium blister packs consisting of 10 and 100 tablets in strips of 10, packed into a printed carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

CIFLOC 250: 34/20.1.1/0308

CIFLOC 500: 34/20.1.1/0309

CIFLOC 750: 34/20.1.1/0310

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

October 2001

10. DATE OF REVISION OF TEXT

13 November 2024