SCHEDULING STATUS S4

PROPRIETARY NAME (AND DOSAGE FORM)

CIFLOC 250 (film-coated tablets)

CIFLOC 500 (film-coated tablets)

CIFLOC 750 (film-coated tablets)

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.

CIFLOC film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and starch. The coating material contains hypromellose, polyethylene glycol 400 and titanium dioxide.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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*).

Pharmacokinetic properties

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 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 %.

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 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.

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.

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.

CONTRAINDICATIONS

Pregnancy and lactation.

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.

Patients who have shown hypersensitivity to ciprofloxacin or any other quinolones, or to any of the inactive ingredients in the formulation (see COMPOSITION).

Concomitant administration of **CIFLOC** and tizanidine (see INTERACTIONS).

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.

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.

WARNINGS AND SPECIAL PRECAUTIONS

CIFLOC should be used with caution as many patients may experience adverse reactions that may be disabling, long-lasting and potentially irreversible.

CIFLOC should be used with caution in patients with a history of convulsive disorders or a history of CNS disorders (see Central Nervous System/Psychiatric below).

Patients should be advised to stop treatment immediately at the first signs of peripheral and central nervous system effects (including peripheral neuropathy, psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion, impairment of vision, hearing, smell and taste) and to contact their medical practitioner for further advice.

Side effects of the musculoskeletal system including tendinitis, tendon rupture, myalgia, muscle weakness, arthralgia and joint swelling may occur (see Musculoskeletal system below).

Crystalluria related to the use of **CIFLOC** has been observed. Patients receiving **CIFLOC** 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 SIDE EFFECTS).

Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels (see INTERACTIONS).

Gastrointestinal System:

In the event of severe and persistent diarrhoea during or after treatment a doctor must be consulted, since this symptom can hide a serious intestinal disease (life-threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment (see SIDE EFFECTS). In such cases **CIFLOC** must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally). Medicines

that inhibit peristalsis are contraindicated in this situation.

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 CONTRAINDICATIONS and SIDE EFFECTS).

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 CONTRAINDICATIONS and SIDE EFFECTS).

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 SIDE EFFECTS).

Hypersensitivity:

In some instances, hypersensitivity and allergic reactions (as listed under SIDE EFFECTS) may occur after the first administration. Anaphylactic/anaphylactoid reactions (e.g. facial, vascular and laryngeal oedema, dyspnoea) can progress to life-threatening shock, in some instances after the first administration. In these cases **CIFLOC** has to be discontinued and medical treatment (e.g. treatment for shock) is required.

Musculoskeletal System

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

Caution is advised as fluoroquinolones, including **CIFLOC**, are associated with an increased risk of tendonitis and tendon rupture in all ages (see CONTRAINDICATIONS and SIDE EFFECTS). 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 CONTRAINDICATIONS).

Photosensitivity

CIFLOC has been shown to produce photosensitivity reactions.

Patients taking **CIFLOC** should avoid direct exposure to excessive sunlight or UV-light (e.g. sunlamps). Therapy should be discontinued if photosensitisation (i.e. sunburn-like reactions) occur.

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 CONTRAINDICATIONS").

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.

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 CONTRAINDICATIONS and SIDE EFFECTS).

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 INTERACTIONS) 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 CONTRAINDICATIONS).

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 DOSAGE AND DIRECTIONS FOR USE).

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 CONTRAINDICATIONS). Renal function should be assessed before initiation of treatment, and monitored during treatment with fluoroquinolones and ACE inhibitors/angiotensin receptor blockers.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with **CIFLOC** (see SIDE EFFECTS). 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 **CIFLOC** in patients with glucose-6-phosphate dehydrogenase deficiency. **CIFLOC** should be avoided in these patients.

Blood glucose disturbances

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. Cases of hypoglycaemic coma have been reported (see SIDE EFFECTS). In diabetic patients, careful monitoring of blood glucose is recommended.

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.

Overgrowth of resistant organisms with prolonged use

Long-term or repeated administration of **CIFLOC** can lead to superinfections with resistant bacteria or yeast-like fungi.

Vision disorders

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

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.

Streptococcal Infections (including Streptococcus pneumoniae)

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

Cytochrome P450

CIFLOC 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). 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 INTERACTIONS). Co-administration of **CIFLOC** and tizanidine is contra-indicated.

Interaction with tests

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

Children and adolescents

CIFLOC is contraindicated in children less than 18 years. In children arthropathy is reported to occur commonly.

Effects on ability to drive and use machines

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

INTERACTIONS

Concomitant administration of **CIFLOC** and tizanidine has been reported to significantly increase the tizanidine plasma concentration. Use of **CIFLOC** with tizanidine is contraindicated (see CONTRAINDICATIONS).

Concurrent administration of **CIFLOC** 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 adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Concomitant administration of **CIFLOC** and clozapine has been reported to increase the plasma concentrations of clozapine and N-desmethylclozapine. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with **CIFLOC** are advised.

Concomitant administration of **CIFLOC** and ropinirole has been reported to increase the mean C_{max} and mean AUC of ropinirole. Monitoring for ropinirole-related side effects and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with **CIFLOC**.

The simultaneous administration of **CIFLOC** and multivalent cation-containing medicines and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g.

sevelamer), sucralfate or antacids and highly buffered medicines (e.g. anti-retrovirals) containing magnesium, aluminium or calcium reduces the absorption of ciprofloxacin.

Consequently, **CIFLOC** should be administered either 1 – 2 hours before, or at least 4 hours after these preparations.

This restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

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

Concomitant administration of the non-steroidal anti-inflammatory drug fenbufen with quinolones, like **CIFLOC**, has been reported to increase the risk of central nervous system stimulation and convulsive seizures.

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

The simultaneous administration of **CIFLOC** and warfarin may intensify the action of warfarin.

Concurrent administration of **CIFLOC** and glibenclamide can intensify the action of glibenclamide (hypoglycaemia) (see WARNINGS AND SPECIAL PRECAUTIONS).

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

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

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

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

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

CIFLOC should be used with caution in patients receiving medicines known to prolong the QT interval (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics,

antihistamines and pentamidine) as **CIFLOC** may have an additive effect on the QT interval (see WARNINGS AND SPECIAL PRECAUTIONS).

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

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**.

PREGNANCY AND LACTATION

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

Mothers taking **CIFLOC** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

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

Dosage and duration of treatment

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.

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

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.

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 and ≤ 60 ml/min/1,73 m^2 • $CL_{cr} \leq 30$ ml/min/1,73 m^2 • Impaired renal function and haemodialysis	Max 1 000 mg/day. Max 500 mg/day. Max 500 mg/day on days after dialysis.
2. Impaired renal function and CAPD (chronic ambulatory peritoneal dialysis) • Oral administration of either ciprofloxacin 500 mg tablet or 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.

SIDE EFFECTS

The following side effects have been observed:

Infections and Infestations:

Frequent: Moniliasis

Less frequent: Pseudomembranous colitis (which may be life-threatening with possible fatal outcomes), moniliasis (oral), moniliasis (gastrointestinal), vaginal moniliasis

Blood and lymphatic system disorders:

Frequent: Eosinophilia, leukopenia

Less frequent: Agranulocytosis, haemolytic anaemia, anaemia, granulocytopenia, leucocytosis, thrombocytopenia, thrombocythaemia (thrombocytosis), pancytopenia, bone marrow suppression

Immune system disorders:

Less frequent: Hypersensitivity reactions, including anaphylactoid (anaphylactic) reaction, allergic reaction, shock (anaphylactic; life threatening), serum sickness like reaction. (See also “Skin and subcutaneous tissue disorders”).

Metabolism and nutrition disorders:

Frequent: Anorexia

Less frequent: Hyperglycaemia, hypoglycaemia (particularly in diabetic patients)

Frequency not known: Hypoglycaemic coma

Psychiatric disorders:

Frequent: Insomnia, agitation, confusion

Less frequent: Hallucination, psychosis, anxiety, abnormal dreams (nightmares), depression

Frequency not known: Nervousness

Nervous system disorders:

Frequent: Headache, dizziness, taste perversion

Less frequent: Migraine, syncope, paraesthesia (peripheral paralgesia), tremor (trembling), Grand mal convulsion, convulsion, intracranial hypertension, ataxia, hyperaesthesia, hypoaesthesia, hypertonia, taste loss (impaired taste), parosmia (impaired smell), anosmia (usually reversible on discontinuation)

Frequency not known: Peripheral neuropathy and polyneuropathy

Eye disorders:

Less frequent: Abnormal vision (visual disturbances), diplopia, chromatopsia

Ear and labyrinth disorders:

Less frequent: Tinnitus, transitory deafness (especially at high frequencies)

Cardiac disorders:

Less frequent: Tachycardia

Frequency not known: ECG QT prolonged, ventricular dysrhythmias (including torsade de pointes)

Vascular disorders:

Frequent: Thrombophlebitis

Less frequent: Hypotension, vasculitis (petechiae, haemorrhagic bullae, papules, crust formation), vasodilation (hot flushes)

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea, larynx oedema

Gastrointestinal disorders:

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

Less frequent: Pancreatitis, dysphagia

Hepato-biliary disorders:

Frequent: Bilirubinaemia

Less frequent: Jaundice, cholestatic jaundice, hepatitis, liver necrosis (very rarely progressing to life-threatening hepatic failure)

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus, maculopapular rash, urticaria

Less frequent: Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's Syndrome), fixed eruption, photosensitivity reaction, pruritic rash, petechia (punctate skin haemorrhages), erythema multiforme (minor), erythema nodosum, oedema (vascular), sweating

Musculoskeletal, connective tissue and bone disorders:

Frequent: Arthralgia (joint pain)

Less frequent: Pain in extremities, back pain, myalgia (muscular pain), joint disorder (joint swelling), tendonitis (predominantly achillo tendonitis), partial or complete tendon rupture (predominantly Achilles tendon), myasthenia, exacerbation of symptoms of myasthenia gravis, twitching

Frequency not known: Tenosynovitis

Renal and urinary disorders:

Less frequent: Acute kidney failure, renal failure, abnormal kidney function, haematuria, crystalluria, interstitial nephritis

General disorders and administration site conditions:

Frequent: Asthenia (general feeling of weakness, tiredness)

Less frequent: Pain, chest pain, drug fever, oedema (peripheral, face), abnormal (unsteady) gait

Frequency not known: Tiredness

Investigations:

Frequent: increased SGOT (AST), increased SGPT (ALT), abnormal liver function test, increased alkaline phosphatase, increased creatinine, increased blood urea

Less frequent: Altered prothrombin values, increased amylase, increased lipase

Post-marketing Experience:

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 cases and/or aortic regurgitation was diagnosed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

CIFLOC 250:	White, oval shaped film-coated tablets debossed with ‘R’ on one side and ‘126’ on other side.
CIFLOC 500:	White, oval shaped, beveled 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.

PRESENTATION

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.

STORAGE INSTRUCTIONS

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.

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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