SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

DYNAFLOC 500 (tablets)

COMPOSITION:

Active ingredient:

Each **DYNAFLOC 500** tablet contains ciprofloxacin hydrochloride monohydrate, equivalent to 500 mg ciprofloxacin.

Inactive ingredients:

Anhydrous colloidal silicon, crospovidone, magnesium stearate, microcrystalline cellulose.

DYNAFLOC tablets are sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A: 20.1.1. Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ciprofloxacin is a synthetic, 4-quinolone derivative with *in vitro* bactericidal activity against the following Gram-negative and Gram-positive organisms. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

Acinetobacter
Aeromonas
Brucella
Campylobacter jejuni
Citrobacter freundii
Citrobacter species
Corynebacterium
E. coli
Edwardsiella
Enterobacter cloacae
Enterobacter species
Haemophilus influenzae
Haemophilus para-influenzae
Hafnia
Klebsiella species
Listeria
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoea
Pasteurella
Plesiomonas
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella enteritidis
Serratia marcescens
Shigella flexneri
Shigella sonnei
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus faecalis
Streptococcus pyogenes
Streptococcus species
Streptococci viridans
Vibrio
Yersinia

The following organisms show varying degrees of *in vitro* sensitivity to ciprofloxacin:

Alcaligenes, Enterococcus faecalis, Flavobacterium, Gardnerella, Legionella, Mycobacterium

fortuitum, Mycobacterium tuberculosis, Mycoplasma hominis, Streptococcus agalactiae, Chlamydia.

The following 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. *Bacteriodes, Treponema pallidum*).

Pharmacokinetic properties:

Ciprofloxacin plasma levels are dose-related and peak 0,5 – 2 hours after oral dosing. The absolute oral bioavailability is approximately 70 % with no substantial loss by first pass metabolism. Distribution of ciprofloxacin is wide and the volume of distribution high, indicating extensive tissue penetration. Ciprofloxacin is present in lung, skin, fat, muscle, cartilage and bone. It is also present in active form in the saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile secretions, prostatic secretions, cerebrospinal fluid and the aqueous humor. Protein binding is low. 40 % to 50 % is excreted in urine as unchanged drug. Approximately 15 % of a single dose of ciprofloxacin is eliminated as metabolites. Elimination occurs primarily by the kidneys and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 ml/minute. The elimination half-life of unchanged ciprofloxacin is 3 – 5 hours. The elimination kinetics are linear; after repeated dosing at 12 hourly intervals and once steady state has been reached no accumulation occurs.

INDICATIONS:

DYNAFLOC is indicated for the treatment of the following infections caused by ciprofloxacin sensitive bacteria:

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Haemophilus para-influenzae*.

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*.

Gastro-intestinal Infections: Infective diarrhoea caused by *E. coli*, *Campylobacter jejuni*, *Shigella flexneri* and *Shigella sonnei*.

Bone Infections: Osteomyelitis due to susceptible Gram-negative organisms.

Gonorrhoea.

DYNAFLOC is ineffective against *Treponema pallidum*.

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

Refer to **WARNINGS AND SPECIAL PRECAUTIONS**.

CONTRAINDICATIONS:

Safety during pregnancy and lactation has not been established.

DYNAFLOC is contraindicated in children under 18 years and in growing adolescents, except where the benefits of treatment exceed the risks. 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.

DYNAFLOC is contraindicated in patients who have shown hypersensitivity to ciprofloxacin or any other quinolones.

Drugs that inhibit peristalsis are contraindicated.

Concomitant use of fluoroquinolones with angiotensin converting enzyme (ACE) inhibitors (e.g. perindopril, enalapril, lisinopril and ramipril) or renin-angiotensin receptor blockers (e.g. losartan, valsartan, irbesartan and telmisartan) is contraindicated in patients with moderate to severe renal impairment.

WARNINGS AND SPECIAL PRECAUTIONS:

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. In diabetic patients, careful monitoring of blood glucose is recommended.

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

In individual cases psychotic reactions (even progressing to self-endangering behaviour) have been reported.

In some instances, these reactions occurred already after the first administration of ciprofloxacin. In these cases, ciprofloxacin has to be discontinued and the doctor should be informed immediately.

Anaphylactic/anaphylactoid reactions (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock) have been reported, in some instances after the first administration. In these cases, ciprofloxacin has to be discontinued and medical treatment (e.g. treatment for shock) is required.

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 (pseudomembranous colitis), requiring immediate treatment. In such cases ciprofloxacin must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 4 x 250 mg/day).

In single cases during the administration of ciprofloxacin, achillotendinitis was observed. Cases of partial or complete rupture of the achilles tendon have been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. Therefore, at any signs of an achillotendinitis (e.g. painful swelling) the administration of ciprofloxacin should be discontinued, and a physician be consulted. Long-term or repeated administration of ciprofloxacin can lead to superinfections with resistant bacteria or yeast-like fungi.

For the indications listed below, fluoroquinolone antibiotics should only be used when other antimicrobials have been considered inappropriate, have failed, are contraindicated or not tolerated (see **INDICATIONS**):

- treating non-severe or self-limiting infections (such as pharyngitis, tonsillitis and acute bronchitis)
- preventing travellers' diarrhoea or recurrent lower urinary tract infections
- non-bacterial infections, e.g. non-bacterial (chronic) prostatitis
- mild to moderate infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease (COPD), acute bacterial rhinosinusitis and acute otitis media).

Musculoskeletal System:

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids. Caution is advised when prescribing for patients with renal impairment and patients with solid organ transplants, as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated in these patients.

At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest. Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Aortic aneurysm and dissection:

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older 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 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 physician in an emergency department.

Caution should be exercised when using **DYNAFLOC** in patients being treated with ACE inhibitors/renin-angiotensin receptor blockers, as concomitant use with fluoroquinolones such as **DYNAFLOC** precipitate acute kidney injury (AKI), especially those with moderate to severe renal impairment and elderly patients (see **CONTRAINDICATIONS** and **INTERACTIONS**). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

Effects on ability to drive and use machines:

Even when the medicine is taken as prescribed, it can affect the speed of reaction to such an extent that the ability to drive or to operate machinery is impaired. This applies particularly in combination with alcohol.

INTERACTIONS:

Concurrent administration of **DYNAFLOC** 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. **DYNAFLOC** tablets should be administered 1 – 2 hours before, or at least 4 hours after taking iron preparations, antacids containing magnesium, aluminium, calcium or sucralfate as interference with absorption may occur. This restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with quinolones 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 transient increases in serum creatinine concentrations have been observed. The simultaneous administration of **DYNAFLOC** and warfarin may intensify the action of warfarin.

In particular cases, concurrent administration of **DYNAFLOC** and glibenclamide can intensify the action of glibenclamide (hypoglycaemia). Probenecid interferes with renal secretion of **DYNAFLOC**. Co-administration of probenecid and **DYNAFLOC** increases the **DYNAFLOC** serum concentrations. Metoclopramide accelerates the absorption of **DYNAFLOC**, resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of **DYNAFLOC**.

Fluoroquinolones such as **DYNAFLOC** should be used with caution in patients being treated with ACE inhibitors/renin-angiotensin receptor blockers, as concomitant use may precipitate acute kidney injury (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**). Use of ACE inhibitors and other medicines that affect renal glomerular filtration, may lead to renal impairment due to altered renal haemodynamics. Increased serum creatinine and blood urea nitrogen may occur, resulting in acute kidney injury.

HUMAN REPRODUCTION:

Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

DYNAFLOC 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 depends upon the severity of the infection, clinical response and bacteriological findings. For acute uncomplicated

cystitis in women, the treatment period is 3 days. Generally, treatment should be continued for at least 3 days after the signs and symptoms of the infection have disappeared. For acute infections the usual treatment period is 5 – 10 days with **DYNAFLOC** tablets. For severe and complicated infections more prolonged therapy may be required. In streptococcal infections the treatment must last at least 10 days because of the risk of late complications.

Infections of the lower respiratory tract: Mild to moderate – 250 to 500 mg twice daily; severe or complicated – 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).

Infections of the urinary tract: Acute uncomplicated cystitis – 250 mg twice daily; mild to moderate – 250 mg twice daily; severe or complicated – 500 mg twice daily.

Infections of the skin: Mild to moderate – 500 mg twice daily; severe or complicated – 750 mg twice daily.

Infectious diarrhoea: 500 mg twice daily.

Bone infections: Mild to moderate – 500 mg twice daily; severe or complicated – 750 mg twice daily. Treatment may be required for 4 – 6 weeks or longer.

Gonorrhoea: A single dose of 250 mg.

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

Impaired Renal or Liver Function: In patients with reduced renal function, the half-life of ciprofloxacin is prolonged, and the dosage needs to be adjusted.

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

Dose adjustment of ciprofloxacin for patients with kidney and/or liver insufficiency.

1.	**Kidney insufficiency:**	
1.1	CLcr > 31 ml/min/1,73 m^2 < 60 ml/min/1,73 m^2	Max 1000 mg/day orally.
1.2	CLcr < 30 ml/min/1,73 m^2	Max 500 mg/day orally.
1.3	Impaired renal function and haemodialysis	As in 1.2 above; on dialysis days after dialysis.
2.	**Impaired renal function and CAPD**	
2.1	Oral administration of either ciprofloxacin film coated tablet as 500 mg tablet or 2 x 250 mg tablets is indicated.	
2.2	For CAPD patients with peritonitis, the recommended daily oral dose is 500 mg 4 times a day.	
3.	**Liver function disturbances:**	No dose adjustment.
4.	**Liver and kidney insufficiency:**	As in 1.1 and 1.2 above.

SIDE EFFECTS

System Organ Class	Frequency	Side effects
Infections and infestations	Less frequent	Superinfections
Blood and lymphatic system disorders	Less frequent	Eosinophilia, leukocytopenia, granulocytopenia, anaemia, thrombocytopenia, leukocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values
Immune system disorders	Less frequent	Anaphylactic/anaphylactoid reactions (e.g. facial, vascular and laryngeal oedema, dyspnea progressing to life-threatening shock)
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia, particularly in diabetic patients, hyperglycaemia, hypoglycaemic coma
Psychiatric disorders	Less frequent	Nervousness, agitation, anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions (even progressing to self-endangering behaviour), suicidal thoughts
Nervous system disorders	Less frequent	Headache, trembling, insomnia, peripheral paralgesia, peripheral neuropathy, unsteady gait, convulsions, increase in intracranial pressure, impaired taste and smell, migraine
Eye disorders	Less frequent	Visual disturbances (e.g. diplopia, colour vision)
Ear and labyrinth disorders	Less frequent	Dizziness, tinnitus, transitory impairment of hearing, especially at high frequencies

Cardiac disorders	Less frequent	Tachycardia
Vascular disorders	Less frequent	Hot flushes
Gastrointestinal disorders	Frequent Less frequent	Nausea, diarrhoea Vomiting, dyspepsia, abdominal pain, flatulence, anorexia
Hepato-biliary disorders	Less frequent	Temporary increase in transaminases, alkaline phosphatases, cholestatic jaundice (especially in patients with previous liver damage), temporary increase in urea, creatinine or bilirubin in the serum, hepatitis, hepatic necrosis very seldom leading to life- threatening hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, drug fever, punctuate skin haemorrhages (petechiae), blister formation with accompanying hemorrhages (hemorrhagic bullae) and small nodules (papules) with crust formation showing vascular involvement (vasculitis), erythema nodosum, erythema exsudativum multiforme (minor), Stevens-Johnson Syndrome, Lyell Syndrome
Musculoskeletal, connective tissue and bone disorders	Less frequent	Joint pain, joint swelling, general feeling of weakness, muscular pains, tendosynovitis, 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), exacerbation of symptoms of myasthenia gravis
Renal and urinary disorders	Less frequent	Interstitial nephritis, transient impairment in kidney function including transient kidney failure, crystalluria, haematuria
General disorders and administrative site conditions	Less frequent	Tiredness, sweating, fainting, photosensitivity

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of acute, excessive oral 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 ciprofloxacin. Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive.

STORAGE INSTUCTIONS:

Store at or below 25 ºC, in a cool, dry place. Protect from light. Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.