APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DYNAFLOC 500 tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

DYNAFLOC tablets are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets.

White or yellowish, 18 mm x 8 mm oblong, biconvex, film coated tablets, scored on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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DYAFLOC 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.

DYNAFLOC 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.

DYNAFLOC is indicated for the treatment of the following infections caused by ciprofloxacin sensitive bacteria, 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*.

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Severe and/or complicated skin and soft tissue infections caused *by Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus 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.

Prophylaxis of invasive infections due to *Neisseria meningitidis* in patients over 18 years of age.

Gonorrhoea.

DYNAFLOC is ineffective against *Treponema pallidum*.

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

Prior treatment, appropriate culture and susceptibility tests should be performed in order to isolate and identify organisms causing infection and to determine their susceptibility to DYNAFLOC. Therapy with DYNAFLOC 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

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. To contain and eradicate infection, the

lowest dose, for the shortest period of time should be prescribed.

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 kidney, urinary tract and abdominal cavity infections, the treatment period is up to 7 days.

For all other infections treatment period is 7 - 14 days.

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.

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 - 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.

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.

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Prophylaxis of invasive infections due to *Neisseria meningitides:* 500mg single dose tablet.

In cases of a mild/moderate/acute and uncomplicated infection, where all other appropriate antimicrobials approved for a similar indication have failed, are contraindicated, or are not well tolerated, the following dosage instructions are advised:

Infections of the lower respiratory tract: 250 mg twice daily

Infections of the urinary tract: 250 mg twice daily

Infections of the skin: 500 mg twice daily

Infectious diarrhoea: 500 mg twice daily

Bone infections: 500 mg twice daily

Special populations

Patients with renal and hepatic impairment

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

Dose adjustment of ciprofloxacin 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 continuous ambulatory peritoneal dialysis (CAPD):**	
2.1 Oral administration of either ciprofloxacin 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.

Elderly patients (> 65 years)

Elderly patients should receive as low a dose as possible; this will depend on the severity of the illness and on the creatinine clearance (see section 4.2 for dose adjustment).

Paediatric population

DYNAFLOC is contraindicated in children below the age of 18 years (see section 4.3).

Method of administration

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

When taken with either dairy products or mineral fortified drinks, a reduction in absorption of ciprofloxacin can be expected. DYNAFLOC should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. milk, yoghurt, and calcium fortified orange juice). However, dietary calcium as part of a meal does not significantly affect ciprofloxacin absorption (see section 4.5).

Missed dose:

Doctors should advise patients who forget to take DYNAFLOC to take a dose as soon as possible but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remains before the next dose, the missed dose should not be taken and treatment then continued with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to ciprofloxacin, any other quinolones or to any of the ingredients of DYNAFLOC (see section 6.1)
- 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 (creatinine clearance ≤ 30 ml/min) and in elderly patients
- 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 (corrected QT 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

- pregnancy and lactation
- 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
- myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients
- concurrent administration with tizanidine (see section 4.5)
- patients with a history of tendon, muscle, joint, central nervous system, epilepsy or psychotic disorders especially those related to previous quinolone/fluoroquinolone use where alternative, appropriate antibiotic choices are available for treatment
- aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available
- patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed, or is not well tolerated.

4.4 Special warnings and precautions for use

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.
Side effects that may be potentially life-threatening are pancytopenia and marrow depression (see section 4.8).

Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels.

Tendinitis, which most frequently involves the Achilles tendon and may lead to tendon rupture, may occur. Patients using corticosteroids, those with a kidney or lung transplant and the elderly are most at risk of tendinitis and tendon rupture. During DYNAFLOC therapy, close monitoring of these patients is therefore necessary. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment must be discontinued immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. Tendinitis and/or tendon rupture may still occur for several months after completion of treatment. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN, also known as Lyell's syndrome) Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with DYNAFLOC (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, DYNAFLOC 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 DYNAFLOC, treatment with DYNAFLOC must not be restarted in this patient at any time.

***Streptococcus pneumoniae* infections**

Due to limited efficacy against *Streptococcus pneumoniae*, DYNAFLOC should not be prescribed for treatment of pneumococcal infections.

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

DYNAFLOC should be used in combination with another appropriate antibacterial medicine for the treatment of severe infections. DYNAFLOC should not be used in staphylococcal infections and infections involving anaerobic bacteria.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly (see section 4.1).

Cardiac disorders

Ciprofloxacin (as in DYNAFLOC) has been associated with QT prolongation (see sections 4.3 and 4.8).

Women tend to have a longer baseline QTc interval compared with men and may be more sensitive to medicines prolonging the QTc interval, such as DYNAFLOC.

Elderly patients may be more susceptible to effects of DYNAFLOC on the QT interval.

Concomitant use 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 if 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

Torsade 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.

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissections, or in the presence of other risk factors or conditions predisposing aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, rheumatoid arthritis, hypertension or known atherosclerosis) (see section 4.3).

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

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

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

Hypersensitivity

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.

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 (pseudomembranous colitis), requiring immediate treatment. In such cases DYNAFLOC must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 4 x 250 mg/day). Medicines that inhibit peristalsis are contraindicated in this situation.

Renal and urinary system

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

Impaired renal function

Since ciprofloxacin is largely excreted unchanged via renal pathway, dose adjustment is needed in patients with 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 DYNAFLOC. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see section 4.8).

There may be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage (see section 4.8).

Musculoskeletal system

Therapy with DYNAFLOC in patients with myasthenia gravis is contraindicated if alternative

appropriate antibiotic choices are available (see section 4.3). Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment (see section 4.3). Nevertheless, in less frequent 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

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 during strenuous physical activity, in patients with renal impairment, patients with solid organ transplants, or in patients concomitantly treated with corticosteroids.

At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued and physical exercise avoided. Care should be taken to keep the affected limb at rest. Corticosteroids should not be used if signs of tendinopathy occur.

Seizures

DYNAFLOC should be used with caution in patients with a history of convulsive disorders as it is known to trigger seizures or lower the seizure threshold.

This is prevalent in patients with epilepsy and in patients who have suffered from previous central nervous system (CNS) disorders (e.g. lowered convulsion threshold, previous history of convulsions, reduced cerebral blood flow, altered brain structure or stroke).

DYNAFLOC 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).

DYNAFLOC should be discontinued should seizures occur.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with DYNAFLOC 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 a potentially irreversible condition (see section 4.8). The recovery process of neuropathy may be prolonged (weeks or months) and full recovery to the pre-treatment status may not occur.

Psychiatric effects

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

Cases of depression or psychotic reactions may progress to suicidal ideations/thoughts and self-injury, such as attempted or completed suicide (see sections 4.3 and 4.8).

In 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.

Photosensitivity

DYNAFLOC has been shown to produce photosensitivity reactions, patients should therefore avoid direct exposure to excessive sunlight or UV light. Therapy should be discontinued if photosensitisation

(i.e. sunburn-like skin reactions) occurs (see section 4.8).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicines which are metabolised via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxanthines, caffeine, duloxetine, ropinirole, clozapine, olanzapine, agomelatine) are administered concomitantly.

Co-administration of DYNAFLOC and tizanidine is contraindicated. Therefore, patients taking these substances concomitantly with DYNAFLOC 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). Increased plasma concentrations associated with specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see section 4.5).

Concomitant use with ACE inhibitors/angiotensin receptor blockers

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 section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolone and ACE inhibitors/angiotensin receptor blockers whether used separately and/or concomitantly.

Interference with biological tests

Ciprofloxacin may interfere with the *Mycobacterium spp*. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking DYNAFLOC.

Influence on laboratory parameters/urinary sediment

DYNAFLOC may cause a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, or a temporary increase in urea, creatinine or bilirubin in the serum. Hyperglycaemia,

hypoglycaemia, crystalluria or haematuria may occur.

Disturbances in blood glucose

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in elderly 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.

Genital tract infections

Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone resistant *Neisseria gonorrhoeae* isolates.

Therefore, DYNAFLOC should be administered for the treatment of gonococcal urethritis or cervicitis only if ciprofloxacin resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial medicine (e.g. a cephalosporin) unless ciprofloxacin resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. DYNAFLOC should be avoided in these patients, however if therapy is deemed necessary, it should be with caution. In this case, potential occurrence of haemolysis should be monitored.

Methotrexate

The concomitant use of DYNAFLOC with methotrexate is not recommended (see section 4.3 and 4.5).

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 section 4.2):

- 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).

Urinary tract infections

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections varies. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections

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

Infections of the bones and joints

DYNAFLOC should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been less frequently reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. DYNAFLOC should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

Inhalational anthrax

Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating medical practitioners should refer to national and/or international consensus documents regarding the treatment of anthrax.

Resistance

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

Paediatric population

DYNAFLOC is contraindicated in children below the age of 18 years (see section 4.3).

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of children and adolescents. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of drug-related arthropathy by 1-year follow-up of 9.0 % and 5.7 % respectively.

4.5 Interaction with other medicines and other forms of interaction

Effects of other products on DYNAFLOC:

Medicines known to prolong QT interval

DYNAFLOC should not be used in patients receiving medicines known to prolong the QT interval (e.g. Class IA and II antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see sections 4.3 and 4.4).

Chelation complex formation

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

Food and dairy products

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

Probenecid

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

Metoclopramide

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.

Omeprazole

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

Effects of DYNAFLOC on other medicines:

Tizanidine

Tizanidine must not be administered together with DYNAFLOC (see section 4.3). In a clinical study with healthy subjects, 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.

Theophylline

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.

Other xanthine derivatives

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

Phenytoin

Simultaneous administration of DYNAFLOC and phenytoin may result in increased or reduced serum levels of phenytoin. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related side effects when DYNAFLOC is discontinued in patients receiving both medicines, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of DYNAFLOC with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of DYNAFLOC. Increased plasma levels of methotrexate may occur, which in turn, may increase the risk of methotrexate associated toxic reactions. Therefore, patients on methotrexate therapy should be carefully monitored when concomitant DYNAFLOC therapy is indicated.

The concomitant use is not recommended (see section 4.4).

NSAIDs

Concomitant administration of nonsteroidal anti-inflammatory medicines, such as fenbufen, with quinolones has been reported to increase the risk of central nervous system stimulation and convulsive seizures.

Ciclosporin

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

Vitamin K antagonists

Simultaneous administration of DYNAFLOC with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient, so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

The INR should be monitored frequently during and shortly after co-administration of DYNAFLOC with a vitamin K antagonist (e.g. warfarin).

Oral antidiabetic medicines

Hypoglycaemia has been reported when DYNAFLOC and oral antidiabetic medicines, mainly sulfonylureas (e.g. glibenclamide, glimepiride), were co-administered (see section 4.8). In particular cases, concurrent administration of DYNAFLOC and glibenclamide can intensify the action of glibenclamide (hypoglycaemia).

Duloxetine

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

Ropinirole

Concomitant use of ropinirole with ciprofloxacin as in DYNAFLOC, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in an increase of Cmax and AUC of ropinirole by 60 % and 84 %, respectively.

Monitoring ropinirole-related side effects and/or dose adjustment as appropriate is recommended during and shortly after co-administration with DYNAFLOC (see Cytochrome P450 in section 4.4).

Lidocaine (Lignocaine)

Concomitant use of lidocaine-(lignocaine)-containing medicines with a moderate inhibitor of CYP450 1A2 isozyme such as DYNAFLOC, reduces the clearance of intravenous lidocaine by 22 % and may

increase the risk for lidocaine side effects.

Clozapine

Serum concentrations of clozapine and N-desmethylclozapine were increased by 29 % and 31 %, respectively after 7 days of concomitant administration of 250 mg ciprofloxacin with clozapine. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with DYNAFLOC are therefore advised (see Cytochrome P450 in section 4.4).

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Caution is advised when prescribing DYNAFLOC concomitantly with sildenafil.

ACE inhibitors and angiotensin receptor blockers

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 sections 4.3 and 4.4). 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.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see 'Cytochrome P450' in section 4.4).

Zolpidem

Co-administration of DYNAFLOC with zolpidem may increase blood levels of zolpidem, concurrent

use is not recommended.

4.6 Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established.

Pregnancy

The safety of DYNAFLOC in pregnant women has not been established and is therefore contraindicated (see section 4.3).

Animal studies have demonstrated that DYNAFLOC may damage the articular cartilage in the foetus.

Breastfeeding

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

Fertility

There is no data on fertility with DYNAFLOC.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

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Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent	Superinfections, candida and other fungal infections, antibiotic associated colitis (with possible fatal outcome)
Blood and lymphatic system disorders	Less frequent	Eosinophilia, leukocytopenia, granulocytopenia, anaemia, thrombocytopenia, leukocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values, neutropenia, thrombocytaemia, agranulocytosis, life-threatening pancytopenia, life-threatening bone marrow depression
Immune system disorders	Less frequent	Anaphylactic/anaphylactoid reactions (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), serum sickness-like reaction
Endocrine disorders	Frequency unknown	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders	Less frequent Frequency unknown	Hypoglycaemia, particularly in diabetic patients, hyperglycaemia, hypoglycaemic coma, decreased appetite and food intake Hypoglycaemia*, hyperglycaemia*, hypoglycaemic coma*

Psychiatric disorders	Less frequent	Nervousness, agitation, anxiety states, nightmares, confusion, disorientation, abnormal dreams, depression and psychotic reactions (either/both even progressing to self-endangering behaviour, suicidal thoughts, attempted or completed suicide), hallucinations, psychomotor hyperactivity
	Frequency unknown	Mania, including hypomania
Nervous system disorders	Less frequent	Headache, dizziness, trembling, insomnia, peripheral paralgesia, unsteady gait, convulsions, intracranial hypertension, impaired taste and smell, migraine, paraesthesia, dysesthesia, hypoaesthesia, tremor, vertigo, hyperaesthesia, pseudotumour cerebri, migraine, disturbed coordination, olfactory nerve disorders
	Frequency unknown	Peripheral neuropathy and polyneuropathy, Guillain-Barre syndrome*
Eye disorders	Less frequent	Visual disturbances (e.g. diplopia, colour vision)
Ear and labyrinth disorders	Less frequent	Tinnitus, transitory impairment of hearing, especially at high frequencies, hearing loss

Cardiac disorders	Less frequent Frequency unknown	Tachycardia Ventricular dysrhythmia and torsades de pointes** (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged, aortic aneurysm* and dissection*
Vascular disorders	Less frequent	Hot flushes, vasodilatation, vasculitis, hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea (including asthmatic condition)
Gastrointestinal disorders	Frequent Less frequent	Nausea, diarrhoea Vomiting, dyspepsia, abdominal pain, flatulence, anorexia, pancreatitis, antibiotic associated diarrhoea including pseudomembranous colitis
Hepatobiliary disorders	Less frequent	Temporary increase in transaminases, alkaline phosphatases, hepatic impairment, 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 Frequency unknown	Rash, pruritus, urticaria, photosensitivity reactions, punctuate skin haemorrhages (petechiae), blister formation erythema nodosum, erythema multiforme, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life threatening) Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
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, 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, tubulointerstitial nephritis
General disorders and administrative site conditions	Less frequent	Tiredness, sweating, unspecific pain, feeling unwell, fever, oedema, gait disturbances

Investigations	Less frequent	Increase in blood alkaline phosphatase, abnormal prothrombin level (increased INR), increased amylase
	Frequency unknown	Increased international normalised ratio (INR)* (in patients treated with Vitamin K antagonist)*

*Post marketing.

**These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

a. Description of selected adverse reactions

Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post-marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor, or played no role in the reported cases where mitral valve and/or aortic valve regurgitation was diagnosed.

Cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, fatigue, psychiatric symptoms, memory impairment, and impairment of hearing, vision, taste and smell) have been reported less frequently in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

There have been less frequent cases of the following side effects reported following treatment with

other fluoroquinolones, which might possibly also occur during treatment with DYNAFLOC: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia.

A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000.

b. Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

In overdose, side effects may be exaggerated or exacerbated (see section 4.8) and include dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria.

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported.

Management of overdose:

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidity to prevent crystalluria 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.

ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones

ATC code: J01MA02

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

Mechanism of action

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
Corynebacterim
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
Staphylococs aureus
Staphylococcus epidermidis
Streptococcus faecalis
Streptococcus pyogenes
Streptococcus species
Streptococci viridans
Vibrio
Yersinia

Ciprofloxacin has a bactericidal action, not only in the proliferation phase but also in the resting phase. During the proliferation phase of a bacterium a segmental twisting and untwisting of the chromosomes take place. An enzyme called DNA gyrase plays a decisive part in this process. Ciprofloxacin inhibits this DNA gyrase in a way that arrests the bacterial metabolism, since vital information can no longer be read from the bacterial chromosome.

Resistance to ciprofloxacin develops slowly and in stages (multiple-step type). Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance that occurs with β-lactam antibiotics, aminoglycosides, and tetracyclines, has not been observed with ciprofloxacin. Plasmid-carrying bacteria are also sensitive to ciprofloxacin. Parallel resistance to other important but chemically different, active substance groups, such as β-lactam antibiotics, aminoglycosides, tetracyclines, macrolide or peptide antibiotics, sulphonamides, trimethoprim or nitrofuran derivatives is not seen with ciprofloxacin.

The following 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*).
DYNAFLOC is ineffective against *Treponema pallidum*.

5.2 Pharmacokinetic properties

Absorption:

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.

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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 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 and 40 % to 50 % is excreted in urine as unchanged medicine.

Biotransformation:

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

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination:

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.

Renal clearance is between 180 - 300 mL/kg/h and the total body clearance is between 480 - 600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism.

1 % of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric population

The pharmacokinetic data in paediatric patients are limited.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Anhydrous colloidal silicon

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Coating: Opadry Y-1-7000

Hypromellose

Macrogol 400

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/Aluminium Blister packs of 10 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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