PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

CIPROFLOXACIN 2 mg/mL (50 mL) FRESENIUS

CIPROFLOXACIN 2 mg/mL (100 mL) FRESENIUS

CIPROFLOXACIN 2 mg/mL (200 mL) FRESENIUS

Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains ciprofloxacin hydrogen sulphate equivalent to 2 mg ciprofloxacin.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless to slightly yellow solution.

The pH-value of the solution for infusion ranges from 3,9 to 4,5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPROFLOXACIN FRESENIUS 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.
CIPROFLOXACIN FRESENIUS 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.

CIPROFLOXACIN FRESENIUS 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 *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.*

Severe and/or complicated urinary tract infections caused by *Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Providencia rettgeri, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus epidermidis, Streptococcus faecalis.*

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

Severe and/or complicated gastrointestinal infections:

Infective diarrhoea caused by *Campylobacter jejuni, Escherichia coli, 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 CIPROFLOXACIN FRESENIUS. Therapy with CIPROFLOXACIN FRESENIUS may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and method of administration

Posology

The dosage of CIPROFLOXACIN FRESENIUS is determined by the severity and type of infections, the sensitivity of the causative organism(s) and the age, mass and renal function of the patient.

***Adults**:*

The usual dose is 100 - 200 mg IV every 12 hours.

For severe and/or complicated infections 400 mg may be administered every 12 hours.

Intravenous therapy should be discontinued as soon as oral CIPROFLOXACIN FRESENIUS therapy can be substituted. The normal duration of intravenous therapy is up to 7 days.

Cystic fibrosis

In cystic fibrosis patients, the normal dose is 200 mg IV every 12 hours. The low body mass of these patients should, however, be taken into consideration when determining dosage (5 - 10 mg/kg/day).

Special Populations:

Geriatric 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).

Patients with impaired renal or liver function:

In patients with reduced renal function, the half-life of CIPROFLOXACIN FRESENIUS may be prolonged.

The dosage needs to be adjusted as shown below.

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

Dose adjustment of CIPROFLOXACIN FRESENIUS for patients with renal or hepatic impairment:

1. Renal impairment

1.1 CL_{CR} ≥ 31 mL/min/1,73 m^2; ≤ 60 mL/min/1,73 m^2 (moderate renal impairment)	Max 800 mg/day intravenously
1.2 CL_{CR} ≤ 30 mL/min/1,73 m^2 (severe renal impairment)	Max 400 mg/day intravenously
1.3 Impaired renal function and haemodialysis	As in 1.2 above; on dialysis days after dialysis

2. Renal impairment and CAPD (chronic ambulatory peritoneal dialysis)

2.1 Addition of CIPROFLOXACIN FRESENIUS solution to the dialysate (intraperitoneal)	50 mg ciprofloxacin per litre of dialysate administered 4 times a day.

3. Hepatic impairment

No dose adjustment.

4. Renal and hepatic impairment

4.1 CL_{CR} ≥ 31 mL/min/1,73 m^2; ≤ 60 mL/min/1,73 m^2 (moderate renal impairment) or serum creatinine concentration between 0,12 and 0,16 mmol/l (1,4 and 1,9 mg/dl)	Max 800 mg/day intravenously
4.2 CL_{CR} ≤ 30 mL/min/1,73 m^2 (severe renal impairment) or serum creatinine concentration equal or higher than 0,17 mmol/l (2,0 mg/dl)	Max 400 mg/day intravenously

Method of administration

CIPROFLOXACIN FRESENIUS should be administered by intravenous infusion over a period of 60 minutes.

Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.6).

4.3 Contraindications

CIPROFLOXACIN FRESENIUS is contraindicated

- in patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or any of the inactive ingredients (listed in section 6.1).
- when used concomitantly 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.

- in pregnancy and lactation (see section 4.6).
- in myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients.
- with concomitant use with tizanidine (see section 4.5).
- if you have 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.
- in 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.
- in 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.
- with concomitant use of fluoroquinolones with ACE inhibitors/ angiotensin-receptor blockers in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in the elderly.

CIPROFLOXACIN FRESENIUS is contraindicated in children under the age of 18 years. There is evidence of damage to the cartilage of weight-bearing joints in immature animals.

4.4. Special warnings and precautions for use

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

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

Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels. The concomitant use of CIPROFLOXACIN FRESENIUS with methotrexate is not recommended (see section 4.5).

Tendinitis may occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids and in patients with a kidney or lung transplant. Close monitoring of these patients is therefore necessary if CIPROFLOXACIN FRESENIUS is prescribed. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with CIPROFLOXACIN FRESENIUS 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.

***Streptococcus pneumoniae* infections**

CIPROFLOXACIN FRESENIUS should not be used for treatment of pneumococcal infections due to limited efficacy against *Streptococcus pneumoniae.*

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

For the treatment of severe infections, CIPROFLOXACIN FRESENIUS should be used in combination with another appropriate antibacterial medicine.

CIPROFLOXACIN FRESENIUS should not be used in staphylococcal infections and infections involving anaerobic bacteria.

Cardiac disorders

Prolongation of the QT interval, sometimes progressing to Torsade de Pointes, has been associated with CIPROFLOXACIN FRESENIUS (see sections 4.3 and 4.8). Women tend to have a longer baseline QTc interval compared to men.

Elderly patients and women may be more sensitive to QTc-prolonging medicines. Therefore, caution should be taken when using CIPROFLOXACIN FRESENIUS in these populations.

Concomitant use of CIPROFLOXACIN FRESENIUS with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if:

- concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or
- symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrhythmias (e.g. class IA or III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics), (see section 4.5) or
- congenital long QT syndrome,

- risk of Torsades de Pointes,
- uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia.

A pre-treatment ECG and frequent follow up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated.

ACE inhibitors and angiotensin-receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3).

Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolone and ACE inhibitors/angiotensin receptor blockers.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

There is an increased risk of aortic aneurysm and dissection, particularly in the elderly population, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

Fluoroquinolones should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see section 4.3).

CIPROFLOXACIN FRESENIUS should only be used after a careful assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in presence of other risk factors or conditions predisposing:

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

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

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.

Vision disorders

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

Children and adolescents

CIPROFLOXACIN FRESENIUS is contraindicated in children below the age of 18 years (see section 4.3). In children, arthropathy is reported to occur commonly (see additional information on special populations in section 4.2).

Hypersensitivity

Hypersensitivity and allergic reactions including anaphylactic/anaphylactoid shock may occur with the first exposure to CIPROFLOXACIN FRESENIUS. Anaphylactic/anaphylactoid reactions in instances can progress to a life-threatening shock. In these cases, CIPROFLOXACIN FRESENIUS must be discontinued and supportive medical treatment e.g. for shock is required.

Skin and appendages

Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking CIPROFLOXACIN FRESENIUS should 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).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with CIPROFLOXACIN FRESENIUS (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, CIPROFLOXACIN FRESENIUS 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 CIPROFLOXACIN FRESENIUS, treatment with CIPROFLOXACIN FRESENIUS must not be restarted in this patient at any time.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

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

Gastrointestinal system

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

Impaired renal function

Since ciprofloxacin is largely excreted unchanged via the 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 FRESENIUS.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with CIPROFLOXACIN FRESENIUS. 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).

Glucose-6-phosphate dehydrogenase deficiency

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

Musculoskeletal system

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

CIPROFLOXACIN FRESENIUS may exacerbate the symptoms of myasthenia gravis.

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with CIPROFLOXACIN FRESENIUS, even within the first 48 hours of treatment.

Inflammation and ruptures of tendon may occur even up to several months after discontinuation of CIPROFLOXACIN FRESENIUS therapy (see section 4.3).

The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.

At any sign of tendinitis (e.g. painful swelling, inflammation) the administration of CIPROFLOXACIN FRESENIUS should be discontinued and physical exercise be avoided.

CIPROFLOXACIN FRESENIUS should not be used in patients with a history of tendon disorders, especially those related to previous exposure to quinolone or fluoroquinolone use (see section 4.3). CIPROFLOXACIN FRESENIUS should only be used in these patients if appropriate alternative antibiotic choices are not available, have failed, are contraindicated, or not tolerated.

Nervous system

CIPROFLOXACIN FRESENIUS is known to trigger seizures or lower the seizure threshold.

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), CIPROFLOXACIN FRESENIUS 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).

If seizures occur, CIPROFLOXACIN FRESENIUS should be discontinued.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including CIPROFLOXACIN FRESENIUS.

Patients on treatment with CIPROFLOXACIN FRESENIUS should be advised to inform their medical practitioner prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see section 4.8).

The recovery process of neuropathy may be prolonged (weeks or months) and full recovery to the pretreatment status may not occur.

Psychiatric side effects

Psychiatric reactions may occur after the first administration of fluoroquinolones, including CIPROFLOXACIN FRESENIUS.

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). Should a patient develop any of these reactions, CIPROFLOXACIN FRESENIUS should be discontinued and appropriate measures instituted.

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP450 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) are administered concomitantly.

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

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/angiotensin-receptor blockers whether used separately or concomitantly.

Local reactions

Phlebitis or thrombophlebitis, local irritation and pain at the site of injection have been reported with intravenous administration of CIPROFLOXACIN FRESENIUS (see section 4.8). Intravenous infusion should be administered by slow infusion over a period of 60 minutes (see section 4.2). These reactions are more frequent if the infusion time is 30 minutes or less, or if small veins on the hand are used. These local skin reactions may resolve upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Interaction with laboratory tests

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

Influence on laboratory parameters/urinary sediment

CIPROFLOXACIN FRESENIUS 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.

Sodium content

CIPROFLOXACIN FRESENIUS solution for infusion contains sodium. In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be considered.

Dysglycaemia

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported (see section 4.8), usually in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine (e.g. glibenclamide) or with insulin.

Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

4.5 Interaction with other medicines and other forms of interaction

Medicines known to prolong QT interval

CIPROFLOXACIN FRESENIUS 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) (see sections 4.3 and 4.4).

Tizanidine

In a clinical study in healthy subjects, there was an increase in tizanidine serum concentrations

(C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect (see section 4.4).

Tizanidine-containing medicines must not be administered together with CIPROFLOXACIN FRESENIUS (see section 4.5).

Theophylline

Concurrent administration of CIPROFLOXACIN FRESENIUS with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related toxicity. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate (see *Cytochrome P450* in section 4.4).

Other xanthine derivatives

Concurrent administration of CIPROFLOXACIN FRESENIUS with caffeine or pentoxifylline-(oxpentifylline)-containing products, may lead to raised serum concentrations of these xanthine derivatives.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving CIPROFLOXACIN FRESENIUS and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related side effects when CIPROFLOXACIN FRESENIUS 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 CIPROFLOXACIN FRESENIUS with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of CIPROFLOXACIN FRESENIUS potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate-associated toxic reactions. The concomitant use of CIPROFLOXACIN FRESENIUS with methotrexate is not recommended (see section 4.4).

NSAID's

Concomitant administration of the non-steroidal anti-inflammatory medicines with quinolones such as CIPROFLOXACIN FRESENIUS may increase the risk of central nervous system stimulation and seizures.

Ciclosporin

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

Vitamin K antagonists

The simultaneous administration of CIPROFLOXACIN FRESENIUS 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 CIPROFLOXACIN FRESENIUS with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).

Oral antidiabetic medicines

Hypoglycaemia has been reported when CIPROFLOXACIN FRESENIUS and oral antidiabetic medicines, mainly sulfonylureas (e.g. glibenclamide, glimepiride), were co-administered (see section 4.8).

Concurrent administration of CIPROFLOXACIN FRESENIUS and glibenclamide-containing medicines may intensify the action of glibenclamide, leading to hypoglycaemia.

Duloxetine

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

Ropinirole

Concomitant use of ropinirole with ciprofloxacin as in CIPROFLOXACIN FRESENIUS, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in an increase of C_{max} 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 CIPROFLOXACIN FRESENIUS (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 CIPROFLOXACIN FRESENIUS, reduces the clearance of intravenous lidocaine by 22 % and may increase the risk for lidocaine side effects.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and *N*-desmethylclozapine were increased by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with CIPROFLOXACIN FRESENIUS are 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 CIPROFLOXACIN FRESENIUS concomitantly with sildenafil.

ACE inhibitors and angiotensin-receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see sections 4.3 & 4.4).

Probenecid

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

Agomelatine

Fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no data are available for a possible interaction with CIPROFLOXACIN FRESENIUS, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see section 4.4).

Zolpidem

Co-administration of CIPROFLOXACIN FRESENIUS may increase blood levels of zolpidem. Concurrent use is not recommended.

4.6 Pregnancy and lactation

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

Pregnancy

The safety of CIPROFLOXACIN FRESENIUS in pregnant women has not been established (see section 4.3). CIPROFLOXACIN FRESENIUS must not be prescribed to pregnant women. Animal studies have demonstrated that CIPROFLOXACIN FRESENIUS may damage the articular cartilage in the fetus.

Lactation

Ciprofloxacin is excreted in breast milk.

Due to the potential risk of articular damage, mothers on CIPROFLOXACIN FRESENIUS should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

CIPROFLOXACIN FRESENIUS can affect the speed of reaction, due to musculoskeletal and/or CNS reactions to such an extent that the ability to drive or to operate machinery is impaired (see section 4.8).

4.8 Undesirable effects

Tabulated list of adverse effects

The frequencies of side effects reported with CIPROFLOXACIN FRESENIUS are summarised in the table below.

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known (could not be established from the available data)**
Infections and Infestations		Candida and other fungal infections, antibiotic associated colitis (with possible fatal outcome)	

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
Blood and Lymphatic System Disorders		Eosinophilia, leukopenia, anaemia, neutropenia, leucocytosis, thrombocytopenia, thrombocytaemia, haemolytic anaemia, agranulocytosis, life-threatening pancytopenia, life-threatening bone marrow depression	
Immune System Disorders		Allergic reaction, allergic oedema / angioedema, anaphylactic reaction, life-threatening anaphylactic shock, serum sickness-like reaction	
Endocrine Disorders			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
Metabolism and Nutrition Disorders		Decreased appetite and food intake, hyperglycaemia, hypoglycaemia, particularly in diabetic patients	Hypoglycaemic coma
Psychiatric Disorders*		Psychomotor hyperactivity / agitation, confusion and disorientation, anxiety reaction, abnormal dreams, depression and/or psychotic reactions (potentially culminating in self-injurious behaviour such as suicidal ideation / thoughts and attempted or completed suicide), hallucinations	Mania, including hypomania

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
Nervous System Disorders*		Headache, dizziness, sleep disorders, taste disorders, paraesthesia, dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo, migraine, disturbed coordination, olfactory nerve (smell) disorders, hyperaesthesia, intracranial hypertension, pseudotumour cerebri	Peripheral neuropathy and polyneuropathy, Guillain-Barré syndrome
Eye Disorders*		Visual disturbances (e.g. diplopia), visual colour distortions	
Ear and Labyrinth Disorders*		Tinnitus, hearing loss, impaired hearing	

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
Cardiac Disorders**		Tachycardia	QT prolongation, ventricular dysrhythmia, Torsades de Pointes (reported predominantly among patients with further risk factors for QT prolongation), aortic aneurysm and dissection
Vascular Disorders**		Vasodilation, hypotension, syncope, vasculitis, phlebitis or thrombophlebitis	
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea (including asthma)	
Gastrointestinal Disorders	Nausea, diarrhoea, vomiting	Abdominal pain, dyspepsia, flatulence, pancreatitis	
Hepatobiliary Disorders	Increase in transaminases	Increased bilirubin, hepatic impairment,	

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
		cholestatic icterus (jaundice), non-infective hepatitis, liver necrosis which may progress to life-threatening hepatic failure	
Skin and Subcutaneous Tissue Disorders	Rash	Pruritus, urticaria, photo-sensitivity reactions, blistering, erythema multiforme, erythema nodosum Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening), punctate skin haemorrhages (petechiae), haemorrhage bullae and papules with signs of vascular involvement	Acute generalised exanthematous pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
		(vasculitis)	
Musculoskeletal and Connective Tissue Disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia, myalgia, arthritis, increased muscle tone and cramping, muscular weakness, tendonitis, tendon rupture (predominantly Achilles tendon), exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment, renal failure, haematuria, crystalluria, tubulointerstitial nephritis	
General Disorders and Administration Site Conditions*	Injection site reaction	Unspecific pain, feeling unwell, asthenia, fever, oedema, sweating (hyperhidrosis), gait	

System Organ Class	Frequent	Less frequent	Frequency not known (could not be established from the available data)
		disturbance	
Investigations		Increase in blood alkaline phosphatase, abnormal prothrombin level (increased INR), increased amylase	Increased International Normalised Ratio (INR) (in patients treated with vitamin K antagonist)

*Very rare 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 tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

**Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Additional information on special populations

Paediatric population

The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (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. Health care providers 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.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

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

Reversible renal toxicity has been reported.

In the event of acute overdosage, the patient should be carefully observed and given supportive treatment, including monitoring of renal function, urinary pH and acidity should be monitored if required to prevent crystalluria. Only a small amount of CIPROFLOXACIN FRESENIUS (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment

Treatment is symptomatic and supportive and adequate hydration must be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Ciprofloxacin is a synthetic 4-quinolone derivative with *in vitro* bactericidal activity against Gram-negative and Gram-positive organisms.

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 takes 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.

Micro-organisms resistant to ciprofloxacin:

Staphylococcus aureus (methicillin-resistant) and *Stenotrophomonas maltophilia, Actinomyces, Enterococcus faecium; Listeria monocytogenes, Mycoplasma genitalium, Ureaplasma urealitycum*, Anaerobic microorganisms (except *Mobiluncus, Peptostreptococcus, Propionibacterium acnes)*.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.

This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to ciprofloxacin or not.
Ciprofloxacin is ineffective against *Treponema pallidum*.

5.2 Pharmacokinetic properties

Absorption:

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

An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 8 hours has been shown to produce an AUC at steady-state equivalent to that produced by a 750 mg oral dose given every 12 hours. A 400 mg IV dose results in a C_{max} similar to that observed with a 750 mg oral dose. An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250 mg oral dose given every 12 hours.

Distribution:

Distribution of ciprofloxacin is wide and the volume of distribution high, indicating extensive tissue penetration. After intravenous administration, ciprofloxacin is present in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile and prostatic secretions. It has also been detected in the lung, skin, fat, muscle, cartilage and bone. Although the medicine diffuses into cerebrospinal fluid (CSF), CSF concentrations are generally less than 10 % of peak serum concentrations. Levels of the medicine in the aqueous and vitreous chambers of the eye are lower than in serum.

Metabolism:

Approximately 15 % of a single dose of ciprofloxacin is eliminated as metabolites. After IV administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10 % of the intravenous dose. The binding of ciprofloxacin to serum proteins is low (20 to 40 %).

Excretion:

The elimination kinetics are linear; after repeated dosing at 12 hourly intervals and once steady state has been reached no accumulation occurs. The serum elimination half-life is approximately 5 - 6 hours and the total clearance is around 35 l/hr.

After intravenous administration, approximately 50 – 70 % of the dose is excreted in the urine as unchanged medicine.

Following a 200 mg IV dose, concentrations in the urine usually exceed 200 µg/mL 0 – 2 hours after dosing and are generally greater than 15 µg/mL 8 – 12 hours after dosing. Following a 400 mg IV dose, urine concentrations generally exceed 400 µg/mL 0 - 2 hours after dosing and are usually greater than 30 µg/mL 8 - 12 hours after dosing. The renal clearance is approximately 22 l/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (< 1 %) is recovered from the bile as unchanged medicine. Approximately 15 % of an IV dose is recovered from the faeces within 5 days after dosing.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH-adjustment), sodium chloride and water for injection.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

Unless compatibility with other infusion solutions or medicines has been confirmed, they should always be administered separately. Signs of incompatibility include precipitation, clouding and discolouration.

Incompatibility will present with all infusion solutions and medicines that are physically or chemically unstable at the pH of the CIPROFLOXACIN FRESENIUS infusion solution (3,9 - 4,5), e.g. penicillins and heparin solutions, especially in combination with solutions adjusted to an alkaline pH.

6.3 Shelf life

KabiPac 100 mg/50 mL: 24 months

KabiPac 200 mg/100 mL: 36 months

KabiPac 400 mg/200 mL: 36 months

Free*flex* bags 100 mg/50 mL; 200 mg/100 mL; 400 mg/200 mL: 36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not refrigerate or freeze.

Protect from light.

Keep the bottle in the outer container until ready to use.

6.5 Nature and contents of container

CIPROFLOXACIN FRESENIUS is packed into:

100 mL and 250 mL KabiPac polyethylene bottles (50 mL and 100 mL solution filled in 100 mL bottlepack® and 200 mL solution filled in 250 mL bottlepack®).

100 mL and 300 mL **Free***flex*® (polypropylene) bags wrapped in an aluminium overpouch (50 mL and 100 mL solution filled in 100 mL bag and 200 mL solution filled in 300 mL bag).

Pack sizes: 1's and 10's.

Not all packs and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

ANY REMAINING SOLUTION MUST BE DISCARDED

CIPROFLOXACIN FRESENIUS is light-sensitive and should always be stored in the cardboard outer carton. No special precautions are, however, required during the 60-minute infusion period.

Compatibility and stability:

CIPROFLOXACIN FRESENIUS is compatible with various intravenous solutions, including sterile water for injections, 0,9 % sodium chloride solution, 5 % and 10 % dextrose solutions, 5 % dextrose with 0,225 % or 0,45 % sodium chloride solutions, Ringer's solution and Ringer's Lactate solution.

When CIPROFLOXACIN FRESENIUS has been mixed with one of the above compatible solutions, for microbiological reasons and light sensitivity, these solutions should be administered shortly after admixture.

7. HOLDER OF CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LTD

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7

Midrand

Gauteng

1685

SOUTH AFRICA

Telephone number: (011) 545 0000

8. REGISTRATION NUMBERS

CIPROFLOXACIN 2 mg/mL (50 mL) FRESENIUS: 45/20.1.1/0797

CIPROFLOXACIN 2 mg/mL (100 mL) FRESENIUS: 45/20.1.1/0798

CIPROFLOXACIN 2 mg/mL (200 mL) FRESENIUS: 45/20.1.1/0799

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 February 2016

10. DATE OF REVISION OF THE TEXT

11 October 2023