APPROVED PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

MOXIFLOXACIN 400 mg/250 ml FRESENIUS solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 bottle or 1 bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride).

1 ml contains 1,6 mg moxifloxacin (as hydrochloride).

Excipient with known effect:

250 ml of solution for infusion contains 747,5 mg (32,5 mmol) sodium (as acetate and as sulphate).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear yellow solution, free from foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MOXIFLOXACIN FRESENIUS is indicated for the treatment of severe and/or complicated infections caused by moxifloxacin-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.

MOXIFLOXACIN 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 moxifloxacin, 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.

- **Respiratory tract infections:**

MOXIFLOXACIN FRESENIUS is indicated for the treatment of the following bacterial respiratory tract infections where 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:

  - Acute exacerbations of chronic obstructive pulmonary disease (COPD) including chronic bronchitis (AECB) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, methicillin-sensitive *Staphylococcus aureus* or *Moraxella catarrhalis*.
  - Community acquired pneumonia (CAP) of mild to moderate severity caused by *Streptococcus pneumoniae* (including CAP caused by penicillin-resistant strains and multi-drug resistant strains), *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae, Klebsiella pneumoniae*, methicillin-sensitive *Staphylococcus aureus* or *Moraxella catarrhalis*.
  - Acute sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis*.

- **Uncomplicated pelvic inflammatory disease** (i.e. infections of female upper genital tract, including salpingitis and endometritis) (not caused by *Neisseria gonorrhoea)* where these

infections are compliant with the indication statement, with special reference to the second part of the statement.

- **Severe and/or complicated skin and skin structure infections** (including diabetic foot infections) caused by methicillin-sensitive *Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Streptococcus agalactiae, Klebsiella pneumoniae, Proteus mirabilis,* or *Enterobacter cloacae.*
- **Severe and/or complicated intra-abdominal infections** including polymicrobial infections such as abscesses.

MOXIFLOXACIN FRESENIUS is indicated for the treatment of the following bacterial infections where these infections are compliant with the indication statement:

- Severe and/or complicated community acquired pneumonia (CAP), including CAP caused by multi-drug resistant strains.
- Severe and/or complicated skin and skin structure infections (including diabetic foot infections).
- Severe and/or complicated intra-abdominal infections including polymicrobial infections such as abscesses.

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 MOXIFLOXACIN FRESENIUS. Therapy with MOXIFLOXACIN 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 recommended dose for MOXIFLOXACIN FRESENIUS is 400 mg once daily for all indications.

Therapy may be initial intravenous administration, followed by oral administration of moxifloxacin as soon as the oral route is feasible.

Moxifloxacin 400 mg tablets and intravenous solution have been studied in clinical trials for up to 21 days (in complicated skin and skin structure infection).

Special populations

Elderly

No adjustment of dosage is required in the elderly.

Children and adolescents

The use of MOXIFLOXACIN FRESENIUS in children and adolescents below the age of 18 years is contraindicated (see section 4.3)

Patients with hepatic impairment

No dosage adjustment is required in patients with impaired liver function (see section 4.3 for use in patients with liver cirrhosis).

Patients with renal impairment

No dose adjustment is required in patients with renal impairment (including creatinine clearance < 30 mL/min/1,73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

Gender

Dosage adjustments based on gender are not necessary.

Method of administration

The infusion solution should be infused intravenously over 60 minutes. It can be administered directly or together with compatible infusion solutions (see section 6.6).

Duration of administration

The duration of treatment to contain and eradicate an infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. In

general, antibiotic therapy should continue for 3 to 4 days after the manifestations of the infection have cleared.

MOXIFLOXACIN FRESENIUS intravenous infusion:

Community acquired pneumonia: The recommended total treatment duration for sequential administration (intravenous followed by oral therapy)	7 to 14 days
Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy)	7 to 21 days
Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy)	5 to 14 days

The recommended duration of treatment for the indication being treated should not be exceeded.

4.3 Contraindications

- Known hypersensitivity to moxifloxacin or other quinolones or any of the excipients of MOXIFLOXACIN FRESENIUS, listed in section 6.1.
- A history of tendon, muscle, joint, nerve, central nervous system or psychiatric disorders especially those related to previous quinolone/fluoroquinolone use where alternative appropriate antibiotic choices are available.
- A history of convulsions, epilepsy or difficult to control epilepsy disorders.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection where alternative choices are available.
- Myasthenia gravis.

- Concomitant use of fluoroquinolones with Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin-receptor blockers (ARBs) in patients with moderate to severe renal impairment (Creatine Clearance ≤ 30 mL/min) and in elderly patients.
- Patients below 18 years of age (there is evidence of damage to the cartilage of weight-bearing joints in immature animals).
- Pregnancy and lactation (see section 4.6).
- Concomitant use with medicines that prolong the QT interval (see section 4.5).
- Congenital or documented acquired QT prolongation.
- Clinically relevant heart failure with reduced left-ventricular ejection fraction.
- Electrolyte disturbances, particularly in uncorrected hypokalaemia.
- Clinically relevant bradycardia.
- Previous history of symptomatic dysrhythmias.
- 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.

Due to limited clinical data in patients with severe hepatic insufficiency (Child-Pugh C), the use of MOXIFLOXACIN FRESENIUS is not recommended in patients with severe hepatic insufficiency. No dosage adjustment is required in patients with mild to moderate hepatic insufficiency (Child-Pugh A & B).

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

THE SAFETY AND EFFECTIVENESS OF MOXIFLOXACIN FRESENIUS IN PAEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED (see sections 4.3 and 4.6.)

Hypersensitivity/allergic reactions

Hypersensitivity and allergic reactions may occur after the first administration. Anaphylactic reactions can progress to a life-threatening shock, in some instances after the first administration. Hypersensitivity and allergic reactions, including life-threatening anaphylactic/anaphylactoid shock may occur with the first exposure of MOXIFLOXACIN FRESENIUS. In these cases, the treatment with MOXIFLOXACIN FRESENIUS should be discontinued and appropriate medical treatment be instituted.

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions

MOXIFLOXACIN AS IN MOXIFLOXACIN FRESENIUS HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN PATIENTS (SEE SECTION 4.3).

MOXIFLOXACIN FRESENIUS SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALAEMIA, AND PATIENTS RECEIVING CLASS 1A (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTIDYSRHYTHMIC MEDICINES (SEE SECTION 4.3).

As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to MOXIFLOXACIN FRESENIUS associated effects on the QT interval (see section 4.3).

As the magnitude of QT prolongation may increase with increasing concentrations of MOXIFLOXACIN FRESENIUS, the recommended dose and the infusion rate (400 mg within 60 minutes) should not be exceeded. However, in patients suffering from pneumonia no correlation between plasma concentrations of MOXIFLOXACIN FRESENIUS and QTc prolongation was observed. QT prolongation may lead to an increased risk of ventricular dysrhythmias including torsades de pointes. In patients with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of MOXIFLOXACIN FRESENIUS 400mg on the QTc interval was 6 ± 26 msec (see section 4.3).

Treatment with MOXIFLOXACIN FRESENIUS should therefore be avoided due to the lack of clinical experience with MOXIFLOXACIN FRESENIUS in these patient populations (see section 4.3):

- in patients with known prolongation of the QT interval
- in patients with uncorrected hypokalaemia
- in patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-dysrhythmic medicines

MOXIFLOXACIN FRESENIUS should be used with caution as an additive effect of MOXIFLOXACIN FRESENIUS on the QT interval cannot be excluded for the following conditions (see section 4.3):

- in patients treated concomitantly with medicines that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants.
- in patients with ongoing dysrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischaemia.
- in patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded.
- in women and elderly patients who may be more susceptible to QTc-prolonging medicines.

<u>Aortic aneurysm and dissection</u>

There is some evidence of 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 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, hypertension, 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.

Mitral valve and/or aortic valve regurgitation

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).

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 fluoroquinolone or ACE inhibitors/Angiotensin-receptor blockers whether used separately and/or concomitantly.

Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin as in MOXIFLOXACIN FRESENIUS (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if symptoms of liver failure 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) and Acute Generalised Exanthematous Pustulosis (AGEP), which could be life-threatening or fatal, have been reported with moxifloxacin (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, MOXIFLOXACIN 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 AGEP with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.

Prevention of photosensitivity reactions

Quinolones have been shown to cause photosensitivity reactions in patients. Patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin, as in MOXIFLOXACIN FRESENIUS.

Patients predisposed to seizures

Seizures may occur with MOXIFLOXACIN FRESENIUS therapy. It should be used with caution in patients with known or suspected central nervous system (CNS) disorders which may predispose to seizures or lower the seizure threshold (see section 4.3).

Antibiotic-associated diarrhoea including colitis

Antibiotic-associated colitis/pseudomembranous colitis e.g. due to *Clostridium difficile*, has been reported with the use of moxifloxacin as in MOXIFLOXACIN FRESENIUS. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of MOXIFLOXACIN FRESENIUS. In this clinical situation adequate therapeutic measures should be initiated immediately. Medicines inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Patients with myasthenia gravis

MOXIFLOXACIN FRESENIUS should not be used in patients with myasthenia gravis (see section 4.3).

Tendinitis and tendon rupture

The oral administration of moxifloxacin as in MOXIFLOXACIN FRESENIUS caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs

revealed permanent lesions of the cartilage. Related quinolone-class medicines also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

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. Tendinitis and/or tendon rupture may still occur for several months after completion of therapy.

Close monitoring of these patients is therefore necessary if they are prescribed MOXIFLOXACIN FRESENIUS. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with MOXIFLOXACIN FRESENIUS must be stopped immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Patients with pelvic inflammatory disease

Moxifloxacin tablets is not recommended for treatment for patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary.

Patients with MRSA infections

MOXIFLOXACIN FRESENIUS is not recommended for the treatment of methicillin-resistant *Staphylococcus aureus (*MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see section 5.1).

Interference with biological tests

MOXIFLOXACIN FRESENIUS therapy may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving MOXIFLOXACIN FRESENIUS.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones including MOXIFLOXACIN FRESENIUS. Patients under treatment with MOXIFLOXACIN FRESENIUS should be advised to inform their doctor 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 to months) and full recovery to the pre-treatment status may not occur.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including MOXIFLOXACIN FRESENIUS. Patients who developed depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts (see section 4.8). In the event that the patient develops these reactions, MOXIFLOXACIN FRESENIUS should be discontinued, and appropriate measures instituted. Caution is recommended if MOXIFLOXACIN FRESENIUS is to be used in psychotic patients or in patients with a history of psychiatric disease (see section 4.3).

Dysglycaemia

Disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with moxifloxacin, as in MOXIFLOXACIN FRESENIUS, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Patients on sodium diet

In patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome) the additional sodium load of the solution for infusion should be considered. For sodium content of the solution for infusion, see section 2.

Information on excipients

MOXIFLOXACIN FRESENIUS contains 747,5 mg (32,5 mmol) sodium per 250 ml bottle. Caution should be exercised when MOXIFLOXACIN FRESENIUS is administered to patients on low sodium diet.

4.5 Interaction with other medicines and other forms of interaction

For the following substances absence of a clinically relevant interaction with MOXIFLOXACIN FRESENIUS was proven: atenolol, ranitidine, calcium supplements, theophylline, ciclosporin, oral contraceptives, glibenclamide, itraconazole, morphine, probenecid. No dose adjustment is necessary for these medicines.

Ranitidine:

The concomitant administration with ranitidine which alters the gastric pH did not change the absorption characteristics of moxifloxacin significantly.

Theophylline:

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected. Hence, no recommendations with respect to theophylline dosing need to be given.

Warfarin:

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with moxifloxacin. Infectious and inflammatory conditions, advanced age and poor general status of the patient are risk factors. International Normalised Ratio (INR) monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives:

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Antidiabetics:

Concomitant administration of moxifloxacin tablets with glibenclamide may result in a decrease of approximately 21 % in the peak plasma concentrations of glibenclamide.

Itraconazole:

The pharmacokinetics of moxifloxacin are not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with moxifloxacin and vice versa.

Digoxin:

The pharmacokinetics of digoxin are significantly influenced by moxifloxacin. After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30 % at steady state without affecting AUC or trough levels. Increased clinical and laboratory monitoring of patients on digitalis therapy is advised.

Morphine:

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin.

Atenolol:

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects, the AUC was marginally increased (by approximately 4 %) and peak concentrations were decreased by 10 %.

Charcoal:

It was reported that concomitant dosing of charcoal with a dose of 400 mg oral or intravenous moxifloxacin reduced systemic availability of moxifloxacin by more than 80 % and 20 % respectively.

Nonsteroidal anti-inflammatory medicines (NSAIDs):

The concomitant administration of a nonsteroidal anti-inflammatory medicine with a quinolone such as moxifloxacin may increase the risks of CNS stimulation and convulsions.

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 classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

4.6 Fertility, pregnancy and lactation

The use of MOXIFLOXACIN FRESENIUS in pregnancy and lactation is contraindicated (see section 4.3).

Pregnancy

The use of MOXIFLOXACIN FRESENIUS during pregnancy is contraindicated (see section 4.3). The safe use of moxifloxacin as in MOXIFLOXACIN FRESENIUS in pregnancy has not been established. Joint injuries have been reported with quinolones. Animal studies have shown reproductive toxicity.

Breastfeeding

The use of MOXIFLOXACIN FRESENIUS is contraindicated in lactation (see section 4.3). Mothers taking MOXIFLOXACIN FRESENIUS should not breastfeed their babies as quinolones are excreted in human milk. Moxifloxacin as in MOXIFLOXACIN FRESENIUS has been shown to cause lesions in the cartilage of the weight-bearing joints of immature animals.

4.7 Effects on ability to drive and use machines

MOXIFLOXACIN FRESENIUS may result in an impairment of the patient's ability to drive or operate machinery due to musculoskeletal and/or central nervous system reactions. Patients should be advised not to drive or operate any machines until they know how treatment with MOXIFLOXACIN FRESENIUS affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in clinical trials and derived from post-marketing reports with moxifloxacin 400 mg daily administered by the intravenous or oral route (intravenous only, sequential [IV/oral] and oral administration) sorted by frequencies are listed below:

Adverse reactions listed under "frequent" were observed with a frequency below 3 % with the exception of nausea and diarrhoea.

Adverse reactions listed under “Frequency unknown” were derived from post-marketing reports, a frequency can therefore not be stated.

b. Tabulated list of adverse reactions

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and Infestations	
Frequent:	Mycotic superinfections
Blood and lymphatic system disorders	
Less frequent:	Anaemia, leukopenia(s), neutropenia, thrombocytopenia, thrombocytaemia, prolonged prothrombin time / increased INR, abnormal partial thromboplastin time (aPTT), increased prothrombin level /decreased INR prothrombin level /INR abnormal, pancytopenia
Immune system disorders	
Frequent:	Allergic reaction, pruritus, rash, urticaria, blood eosinophilia
Less frequent:	Anaphylactic / anaphylactoid reaction, allergic oedema /angioedema (incl. laryngeal oedema, potentially life- threatening), anaphylactic/ anaphylactoid shock (potentially life-threatening)
Endocrine disorders	
Less frequent:	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

Less frequent:	Hyperlipidaemia, hyperglycaemia, hyperuricaemia, hypoglycaemia, particularly in diabetic patients, hypoglycaemic coma

Psychiatric disorders

Less frequent:	Anxiety reactions, psychomotor hyperactivity/agitation, emotional lability, depression (culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts), hallucinations, depersonalisation, psychotic reactions (culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts), delirium
Frequency unknown:	Behavioural disturbances: potential culmination of depression and psychotic reactions in self- endangering behaviour

Nervous system disorders

Frequent:	Headache, dizziness
Less frequent:	Paraesthesia and dysaesthesia, taste disorders (incl. ageusia in very rare cases), confusion and disorientation, sleep disorders, tremor, vertigo, somnolence, hypoaesthesia, smell disorders (incl. anosmia), abnormal dreams, disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo), seizures of various clinical manifestations (incl. grand mal convulsions), disturbed attention, speech disorders, amnesia, peripheral neuropathy and polyneuropathy, hyperaesthesia
Frequency unknown:	Increased neurological activities: Disturbed coordination leading to fall with injuries, especially in the elderly; Guillain-Barré syndrome

Eye disorders

Less frequent:	Visual disturbances (especially in the course of CNS reactions), transient loss of vision (especially in the course of CNS reactions)

Ear and labyrinth disorders

Less frequent:	Tinnitus, hearing impairment, including deafness (usually reversible)
Cardiac disorders	
Frequent:	QT prolongation in patients with hypokalaemia
Less frequent:	QT prolongation, palpitations, tachycardia, ventricular tachydysrhythmias, syncope, unspecified dysrhythmias
Frequency unknown:	Ventricular dysrhythmias: Torsade de Pointes, cardiac arrest (especially in patients with severe underlying dysrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia); aortic aneurysm and dissection, unspecified dysrhythmias
Vascular disorders	
Less frequent:	Vasodilatation, hypertension, hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Dyspnoea (including asthmatic conditions)
Gastrointestinal disorders	
Frequent:	Nausea, vomiting, gastrointestinal and abdominal pains, diarrhoea
Less frequent:	Decreased appetite and food intake, constipation, dyspepsia, flatulence, gastroenteritis (excl. erosive gastroenteritis), increased amylase, dysphagia, stomatitis, antibiotic-associated colitis/ pseudomembranous colitis (in very rare cases associated with life-threatening complications), *Clostridium difficile*-associated disease (CDAD)
Hepato-biliary disorders	
Frequent:	Increase in transaminases
Less frequent:	Hepatic impairment (incl. LDH increase) increased bilirubin, increased gamma- glutamyl-transferase, increase in blood alkaline phosphatase, jaundice, hepatitis (predominantly cholestatic),

	fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)
Skin and subcutaneous tissue disorders	
Less frequent	Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic epidermal necrolysis (potentially life- threatening)
Frequency unknown:	Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Less frequent:	Arthralgia, myalgia, tendinitis, increased muscle tone and cramping, muscular weakness, tendon rupture, arthritis, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis
Frequency unknown:	Rhabdomyolysis
Renal and urinary disorders	
Less frequent:	Dehydration (caused by diarrhoea or reduced fluid intake), renal impairment, renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)
General disorders and administration site conditions	
Frequent:	Injection and infusion site reactions
Less frequent:	Feeling unwell, unspecific pain, sweating, infusion site thrombophlebitis, oedema

The following adverse reactions have a higher frequency category in the subgroup of intravenously-treated patients, with or without subsequent oral therapy:

Frequent:	Increased gamma-glutamyl-transferase
Less frequent:	Ventricular tachydysrhythmias, hypotension, oedema, antibiotic-associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4),

seizures of various clinical manifestations (incl. grand mal convulsions (see section 4.4)), hallucination, renal impairment and renal failure (due to dehydration especially in elderly with pre-existing renal disorders).

Cases of mitral valve and/or aortic 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.

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 asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Adverse reactions may be exaggerated or exacerbated.

Management

No specific countermeasures after accidental overdosage are recommended. General symptomatic and supportive therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg intravenous MOXIFLOXACIN FRESENIUS will reduce systemic availability of the medicine by more than 20 %. MOXIFLOXACIN FRESENIUS causes QT prolongation in a dose-dependent manner. Patients should be carefully monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA14

Moxifloxacin is a fluoroquinolone antibacterial substance with a broad spectrum of bactericidal action.

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative micro-organisms.

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination.

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Frequently resistant organisms

Aerobic Gram-positive micro-organisms

Enterococcus faecalis

Aerobic Gram-negative micro-organisms

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Proteus mirabilis

Anaerobic micro-organisms

Bacteroides fragilis

Inherently resistant organisms

Aerobic Gram-negative micro-organisms

Pseudomonas aeruginosa

Resistant organisms

Staphylococcus aureus (methicillin/ofloxacin resistant strains), coagulase negative Staphylococci (*S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans*) methicillin-resistant strains.

5.2 Pharmacokinetic properties

Absorption

After a single 400 mg intravenous 1 hour infusion, peak plasma concentrations of approximately 4,1 mg/L were observed at the end of the infusion corresponding to about 26 % higher concentrations than those after oral administration (3,1 mg/L). The AUC value of approximately 39 mg.h/L after intravenous administration is only slightly higher than that observed after oral administration (35 mg.h/L) in accordance with the absolute bioavailability of approximately 91 %. In patients, mean peak plasma concentrations of 4,4 mg/L were observed at steady state.

Pharmacokinetic studies with the oral tablet and intravenous solution have therefore shown the two dosage forms are bioequivalent with respect to the systemic exposure pharmacokinetic parameter AUC.

Distribution

Moxifloxacin is distributed to extravascular spaces. Exposure to the medicine in terms of AUC (AUCnorm = 6 kg*h/L) is high; the volume of distribution at steady state amounts to Vss of approximately 2 L/kg. In saliva peak concentrations and similar to those of plasma may be reached. Due to low protein binding (approximately 45 %) high free peak concentrations >10 x MIC are observed. In *in-vitro* and *ex-vitro* experiments, the degree of protein binding within the moxifloxacin plasma concentration range of 0,02 to 2 mg/L remained the same at approximately 45 %, independent of the concentration of the medicine. Moxifloxacin is mainly bound to serum albumin.

In tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polyps) and inflamed lesions (cantharide blister fluid) concentrations exceeding those of the plasma are reached.

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of medicine administration after a single dose of 400 mg moxifloxacin.

Biotransformation

Moxifloxacin undergoes phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged medicine as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

Elimination

Moxifloxacin is eliminated from plasma and saliva with a mean terminal half-life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Renal clearance amounts to about 24-53 mL/min suggesting partial tubular reabsorption of the medicine from the kidneys. Approximately 19 % of the dose is excreted unchanged into the urine and approximately 25 % in the faeces. About 2,5 % is recovered as M1 in the urine and 36 % in the faeces, respectively. About 14% is recovered as M2 in the urine.

Linearity/non-linearity

Pharmacokinetics are linear up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate

Disodium sulphate

Water for injection

Sulphuric acid (for pH-adjustment).

6.2 Incompatibilities

The following solutions are incompatible with MOXIFLOXACIN FRESENIUS solution for infusion:

- Sodium chloride 10 % and 20 % solutions (precipitation can occur at higher ratios)
- Sodium bicarbonate 4,2 % and 8,4 % solutions (causes pH shift, and CO_2 bubbles can form).

MOXIFLOXACIN FRESENIUS must not be mixed with other medicines except those mentioned in section 6.6.

Do not use if the solution is cloudy.

6.3 Shelf life

3 years

Use immediately after first opening and/or dilution.

6.4 Special precautions for storage

Store at or below 30 °C in the original packaging and protect from light (keep bags in their overwraps until required for use). Do not store below 15 °C. At temperatures below 15 ºC precipitation may occur, which will re-dissolve at room temperature (15 ºC to 25 ºC). It is therefore recommended not to store the infusion solution in a refrigerator. Protect from light. Keep the flexibags in the overwrap/pouch or the bottles in the outer cartons until required for use.

MOXIFLOXACIN FRESENIUS should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

6.5 Nature and contents of container

Two packing systems are provided:

• A 300 ml polyolefin bags (**Free***flex*®) bags with polypropylene port sealed in aluminium foil overwrap.

• The ***KabiPac***® packaging system consists of a primary container of 250 ml low density polyethylene blow-fill-seal bottle. The container's head is protected by a secondary packaging closure, consisting of HDPE/LDPE.

Pack sizes: 1, 20, 25 and 40.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

MOXIFLOXACIN FRESENIUS is for single use only and any remaining portion must be discarded in accordance with local regulations.

If medically indicated the solution for infusion can be administered via a T-tube, together with the following compatible infusion solutions:

- Water for injections
- Sodium chloride 0,9 %
- Dextrose 5 %
- Dextrose 10 %
- Ringer lactate solution

MOXIFLOXACIN FRESENIUS solution for infusion should not be co-infused with other medicines; each medicine should be given separately.

Only clear solutions should be used. The solution for infusion must be inspected before use. Do not use if there is any visible particulate matter or if the solution is cloudy.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand No. 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7, 1685

8. REGISTRATION NUMBER

49/20.1.1/0965

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 22 June 2021

10. DATE OF REVISION OF THE TEXT

27 June 2022