Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Moxifloxacin 400 mg/250 ml Solution for Infusion, FreeFlex bags

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride).

Each ml contains 1.6 mg moxifloxacin (as hydrochloride).

Excipient with known effect:
250 ml of solution for infusion contains 54.4 mmol sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear yellow solution.
pH of solution is between 5.0 and 6.0.
Osmolality of solution: 260 – 330 mOsm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Moxifloxacin is indicated for the treatment of:

- Community acquired pneumonia (CAP)

- Complicated skin and skin structure infections (cSSSI)

Moxifloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
The recommended dose is 400 mg moxifloxacin, infused once daily.

Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400 mg tablets, when clinically indicated.

In clinical studies most patients switched to oral therapy within 4 days (CAP) or 6 days (cSSSI). The recommended total duration of intravenous and oral treatment is 7 - 14 days for CAP and 7 - 21 days for cSSSI.

Renal/hepatic impairment

No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis (see section 5.2 for more details).

There is insufficient data in patients with impaired liver function (see section 4.3).

Other special populations

No adjustment of dosage is required in the elderly and in patients with low bodyweight.

Paediatric population
Moxifloxacin is contraindicated in children and growing adolescents. Efficacy and safety of moxifloxacin in children and adolescents have not been established (see sections 4.3, 4.4 and 5.3).

Method of administration

For intravenous use; **constant infusion over 60 minutes** (see also section 4.4).

If medically indicated the solution for infusion can be administered via a T-tube, together with compatible infusion solutions (see section 6.6).

4.3 Contraindications

• Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients listed in section 6.1.
• Pregnancy and lactation (see section 4.6).
• Patients below 18 years of age.
• Patients with a history of tendon disease/disorder related to quinolone treatment.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin is therefore contraindicated in patients with:

• Congenital or documented acquired QT prolongation
• Electrolyte disturbances, particularly in uncorrected hypokalaemia
• Clinically relevant bradycardia
• Clinically relevant heart failure with reduced left-ventricular ejection fraction
• Previous history of symptomatic arrhythmias

Moxifloxacin should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN.

4.4 Special warnings and precautions for use

The use of Moxifloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence
Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, 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).
Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or 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 physician 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. The benefit of moxifloxacin treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section.

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

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not be exceeded. For more details see below and refer to sections 4.3 and 4.5.

Treatment with moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.

Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischaemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. See also sections 4.3 and 4.5.

Moxifloxacin should be used with caution in patients who are taking medications that can reduce potassium levels. See also sections 4.3 and 4.5.

Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia. See also section 4.3.

Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as moxifloxacin and therefore special caution is required.

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. Moxifloxacin 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.

Hypersensitivity / allergic reactions

Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In cases of clinical manifestations of severe hypersensitivity reactions moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.

Liver function tests/investigations should be performed in cases where indications of liver dysfunction 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 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 should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN, AGEP or DRESS with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.

Patients predisposed to seizures

Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold. In case of seizures, treatment with moxifloxacin should be discontinued and appropriate measures instituted.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with moxifloxacin 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).

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases 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 should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Antibiotic-associated diarrhoea incl. colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Patients with myasthenia gravis

Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Tendinitis, tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Patients with renal impairment

Elderly patients with renal disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.

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).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitivity reactions

Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Nevertheless patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin (see section 4.8).

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with a family history of or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.

Peri-arterial tissue inflammation

Moxifloxacin solution for infusion is for intravenous administration only. Intra-arterial administration should be avoided since preclinical studies demonstrated peri-arterial tissue inflammation following infusion by this route.

Patients with special cSSSI

Clinical efficacy of moxifloxacin in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

Patients on sodium diet

This medicinal product contains 1206 mg sodium per dose, equivalent to 60% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interference with biological tests

Moxifloxacin 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.

Patients with MRSA infections

Moxifloxacin is not recommended for the treatment of 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).

Paediatric population

Due to adverse effects on the cartilage in juvenile animals (see section 5.3) the use of moxifloxacin in children and adolescents < 18 years is contraindicated (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products

An additive effect on QT interval prolongation of moxifloxacin and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore, co-administration of moxifloxacin with any of the following medicinal products is contraindicated (see also section 4.3):

• anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
• anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
• antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
• tricyclic antidepressive agents
• certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
• certain antihistaminics (terfenadine, astemizole, mizolastine)
• others (cisapride, vincamine IV, bepridil, diphemanil).

Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels (e.g. loop and thiazide-type diuretics, laxatives and enemas [high doses], corticosteroids, amphotericin B) or medication that is associated with clinically significant bradycardia.

After repeated dosing in healthy volunteers, moxifloxacin increased C_{max} of digoxin by approximately 30% without affecting AUC or trough levels. No precaution is required for use with digoxin.

In studies conducted in diabetic volunteers, concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of approximately 21% in the peak plasma concentrations of glibenclamide. The combination of glibenclamide and moxifloxacin could theoretically result in a mild and transient hyperglycaemia. However, the observed pharmacokinetic changes for glibenclamide did not result in changes of the pharmacodynamic parameters (blood glucose, insulin). Therefore, no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

Changes in INR

A large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibacterial agents, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. The infectious and inflammatory conditions, age and general status of the patient appear to be risk factors. Under these circumstances, it is difficult to evaluate whether the infection or the treatment caused the INR (international normalised ratio) disorder. A precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Clinical studies have shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole.

In vitro studies with human cytochrome P450 enzymes supported these findings. Considering these results a metabolic interaction via cytochrome P450 enzymes is unlikely.

Interaction with food

Moxifloxacin has no clinically relevant interaction with food including dietary products.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of moxifloxacin in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals and reversible joint injuries described in children receiving some fluoroquinolones, moxifloxacin must not be used in pregnant women (see section 4.3).

Breastfeeding
There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals, breast-feeding is contraindicated during moxifloxacin therapy (see section 4.3).

Fertility
Animal studies do not indicate impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness; acute, transient loss of vision, see section 4.8) or acute and short lasting loss of consciousness (syncope, see section 4.8). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

4.8 Undesirable effects

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:

Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000
Not known frequency cannot be estimated from the available data

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**Very Rare** < 1/10,000	Not known (frequency cannot be estimated from the available data)
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis				
Blood and lymphatic system disorders		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged / INR increased		Prothrombin level increased / INR decreased Agranulocytosis Pancytopenia	
Immune system disorders		Allergic reaction (see section 4.4)	Anaphylaxis incl. very rarely life-threatening shock (see section 4.4) Allergic oedema / angioedema (incl. laryngeal oedema, potentially life-threatening, see section 4.4)		
Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition		Hyperlipidaemia	Hyperglycaemia Hyperuricemia	Hypoglycaemia Hypoglycaemic	

disorders				coma	
Psychiatric disorders*		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4) Hallucination Delerium	Depersonalization Psychotic reactions (potentially culminating in self- injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4)	
Nervous system disorders*	Headache Dizziness	Par- and Dysaesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions (see section 4.4) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia	
Eye disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)	Photophobia	Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7) Uveitis and bilateral acute iris transillumination (see section 4.4)	
Ear and labyrinth disorders*			Tinnitus Hearing impairment incl. deafness (usually reversible)		
Cardiac disorders	QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de Pointes (see section 4.4) Cardiac arrest (see section 4.4)	
Vascular		Vasodilatation	Hypertension	Vasculitis	

disorders			Hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)			
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic-associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications, see section 4.4)		
Hepatobiliary disorders	Increase in transaminases	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, see section 4.4)	
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria Dry skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see section 4.4)	Acute Generalised Exanthematous Pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption, Photosensitivity reactions (see section 4.4)
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendonitis (see section 4.4) Muscle cramp Muscle twitching Muscle weakness	Tendon rupture (see section 4.4) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)	Rhabdomyolysis
Renal and urinary disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure (see section 4.4)		
General disorders and administration	Injection and infusion site reactions	Feeling unwell (predominantly asthenia or fatigue)	Oedema		

site conditions*		Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating Infusion site (thrombo-) phlebitis			

*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, and neuralgia, , fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration impairment, 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).**

The following undesirable effects have a higher frequency category in the subgroup of IV treated patients with or without subsequent oral therapy:
Common: Increased gamma-glutamyl-transferase
Uncommon: Ventricular tachyarrhythmias, hypotension, oedema, antibiotic-associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4), seizures incl. grand mal convulsions (see section 4.4), hallucination, renal impairment (incl. increase in BUN and creatinine), renal failure (see section 4.4)

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the
HPRA Pharmacovigilance
www.hpra.ie

4.9 Overdose

No specific countermeasures after accidental overdose are recommended. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Concomitant administration of charcoal with a dose of 400 mg oral or intravenous moxifloxacin will reduce systemic availability of the drug by more than 80% or 20% respectively. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Moxifloxacin inhibits bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) that are required for bacterial DNA replication, transcription and repair.

Pharmacokinetic/pharmacodynamic relationship
Fluoroquinolones exhibit a concentration dependent killing of bacteria. Pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials indicate that the primary determinant of efficacy is the AUC24/MIC ratio.

Mechanism of resistance

Resistance to fluoroquinolones can arise through mutations in DNA gyrase and topoisomerase IV. Other mechanisms may include over-expression of efflux pumps, impermeability, and protein-mediated protection of DNA gyrase. Cross resistance should be expected between moxifloxacin and other fluoroquinolones.

The activity of moxifloxacin is not affected by mechanisms of resistance that are specific to antibacterial agents of other classes.

Breakpoints

EUCAST clinical MIC and disk diffusion breakpoints for moxifloxacin (01.01.2012):

Organism	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 0.5 mg/l ≥ 24 mm	> 1 mg/l < 21 mm
S. pneumoniae	≤ 0.5 mg/l ≥ 22 mm	> 0.5 mg/l < 22 mm
Streptococcus Groups A, B, C, G	≤ 0.5 mg/l ≥ 18 mm	> 1 mg/l < 15 mm
H. influenzae	≤ 0.5 mg/l ≥ 25 mm	> 0.5 mg/l < 25 mm
M. catarrhalis	≤ 0.5 mg/l ≥ 23 mm	> 0.5 mg/l < 23 mm
Enterobacteriaceae	≤ 0.5 mg/l ≥ 20 mm	> 1 mg/l < 17 mm
Non-species related breakpoints*	≤ 0.5 mg/l	> 1 mg/l
* Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined.		

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus**+ *Streptococcus agalactiae* (Group B) *Streptococcus milleri* group* (*S. anginosus, S. constellatus and S. intermedius*) *Streptococcus pneumoniae** *Streptococcus pyogenes** (Group A) *Streptococcus viridans* group *(S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus)*
Aerobic Gram-negative micro-organisms *Acinetobacter baumanii* *Haemophilus influenzae** *Legionella pneumophila* *Moraxella (Branhamella) catarrhalis**
Anaerobic micro-organisms *Prevotella* spp.
"Other" micro-organisms *Chlamydophila (Chlamydia) pneumoniae** *Coxiella burnetii* *Mycoplasma pneumoniae**
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecalis**

*Enterococcus faecium**
Aerobic Gram-negative micro-organisms *Enterobacter cloacae** *Escherichia coli**[#] *Klebsiella oxytoca* *Klebsiella pneumoniae**[#] *Proteus mirabilis**
Anaerobic micro-organisms *Bacteroides fragilis**
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Pseudomonas aeruginosa*
*Activity has been satisfactorily demonstrated in clinical studies. [+]Methicillin resistant *S. aureus* have a high probability of resistance to fluoroquinolones. Moxifloxacin resistance rate of > 50% have been reported for methicillin resistant *S. aureus*. [#]ESBL-producing strains are commonly also resistant to fluoroquinolones.

5.2 Pharmacokinetic properties

Absorption and Bioavailability
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 a mean increase of approximately 26% relative to those seen after oral administration (3.1 mg/l). The AUC value of approximately 39 mg·h/l after i.v. 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, there is no need for age or gender related dose adjustment on intravenous moxifloxacin.

Pharmacokinetics are linear in the range of 50 - 1200 mg single oral dose, up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

Distribution
Moxifloxacin is distributed to extravascular spaces rapidly. The steady-state volume of distribution (Vss) is approximately 2 l/kg. In vitro and ex vivo experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

Maximum concentrations of 5.4 mg/kg and 20.7 mg/l (geometric mean) were reached in bronchial mucosa and epithelial lining fluid, respectively, 2.2 h after an oral dose. The corresponding peak concentration in alveolar macrophages amounted to 56.7 mg/kg. In skin blister fluid concentrations of 1.75 mg/l were observed 10 h after intravenous administration. In the interstitial fluid unbound concentration time profiles similar to those in plasma were found with unbound peak concentrations of 1.0 mg/l (geometric mean) reached approximately 1.8 h after an intravenous dose.

Biotransformation
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal (approximately 40%) and biliary/faecal (approximately 60%) pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

In clinical Phase I and in vitro studies no metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes were observed. There is no indication of oxidative metabolism.

Elimination
Moxifloxacin is eliminated from plasma 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. Following a 400 mg intravenous infusion recovery of unchanged drug from urine was approximately 22% and from faeces approximately 26%. Recovery of the dose (unchanged drug and metabolites) totalled to approximately 98% after intravenous administration of the drug. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

Renal impairment

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance > 20 ml/min/1.73 m2). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 m2).

Hepatic impairment
On the basis of the pharmacokinetic studies carried out so far in patients with liver failure (Child Pugh A, B), it is not possible to determine whether there are any differences compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas exposure to parent drug was comparable to exposure in healthy volunteers. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

5.3 Preclinical safety data

In conventional repeated dose studies moxifloxacin revealed haematological and hepatic toxicity in rodents and non-rodents. Toxic effects on the CNS were observed in monkeys. These effects occurred after the administration of high doses of moxifloxacin or after prolonged treatment.

In dogs, high oral doses (≥ 60 mg/kg) leading to plasma concentrations ≥ 20 mg/l caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

After intravenous administration findings indicative of systemic toxicity were most pronounced when moxifloxacin was given by bolus injection (45 mg/kg) but they were not observed when moxifloxacin (40 mg/kg) was given as slow infusion over 50 minutes.

After intra-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

Moxifloxacin was genotoxic in *in vitro* tests using bacteria or mammalian cells. In *in vivo* tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

In vitro, moxifloxacin revealed cardiac electrophysiological properties that can cause prolongation of the QT interval, even though at high concentrations.

After intravenous administration of moxifloxacin to dogs (30 mg/kg infused over 15, 30 or 60 minutes) the degree of QT prolongation was clearly depending on the infusion rate, i.e. the shorter the infusion time the more pronounced the prolongation of the QT interval. No prolongation of the QT interval was seen when a dose of 30 mg/kg was infused over 60 minutes.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations.

Quinolones, including moxifloxacin, are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate,
Sodium sulfate, anhydrous,
Sulfuric acid (for pH-adjustment),
Water for injections

6.2 Incompatibilities

The following solutions are incompatible with moxifloxacin solution for infusion:

Sodium chloride 10% and 20% solutions
Sodium bicarbonate 4.2% and 8.4% solutions
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze.

For storage conditions of the opened/diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Moxifloxacin is packed in:
Polyolefine bags (freeflex) with an administration port (infusion port) and addition port (injection port) consisting of a polypropylene housing and an aluminium-overpouch.

Pack sizes:
Polyolefine bags (freeflex): 1, 10, 20, 25 and 40

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product is for single use only. Any unused solution should be discarded.

The following co-infusions were found to be compatible with moxifloxacin 400 mg/250 ml solution for infusion:

Water for injections, Sodium chloride 0.9%, Glucose 5%/10%, Ringer's solution, Compound Sodium Lactate Solution (Hartmann's Solution, Ringer-Lactate Solution).

Moxifloxacin solution for infusion should not be co-infused with other medicinal products.

Do not use if there are any visible particulate matter or if the solution is cloudy.

At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution below 8°C.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/013/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th January 2014
Date of last renewal: 27th November 2018

10 DATE OF REVISION OF THE TEXT

February 2025