Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Mofloxine 400mg/250ml Solution for IV Infusion

2. Qualitative and quantitative composition

Each 250 mL solution for infusion contains 440 mg Moxifloxacin hydrochloride, equivalent to 400 mg Moxifloxacin.

Excipient of known effect
The solution for infusion (250 mL) contains 2000mg of sodium.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion
Green Yellowish, clear solution.
pH 4.0 - 5.0

4. Clinical particulars

4.1 Therapeutic indications

Mofloxine is indicated for the treatment of the following bacterial infections caused by susceptible strains:

- Bronchitis (acute exacerbations of chronic bronchitis)
- Pneumonia (community acquired)
- Sinusitis (acute)
- Complicated skin and skin structure infections (including
- diabetic foot infections)
- Complicated intra-abdominal infections including polymicrobial infections such as abscesses

Consideration should be given to available 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.
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. hemodialysis and continuous ambulatory peritoneal dialysis.
There is insufficient data in patients with impaired liver function.

Other special populations:

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

Pediatrics population:

Moxifloxacin is contraindicated in children and growing adolescents.
Efficacy and safety of Moxifloxacin in children and adolescents have not been established.

Method of administration:

For intravenous use; constant infusion over 60 minutes. If medically indicated the solution for infusion can be administered via a T-tube, together with compatible infusion solutions.

4.3 Contraindications

Known hypersensitivity to moxifloxacin or other quinolones or any of the excipients.
Pregnancy and lactation.
Patients below 18 years of age.

4.4 Special warnings and precautions for use

Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system and musculoskeletal system.

Hypersensitivity

In some instances, the hypersensitivity and allergic reactions occurred after the first administration and the doctor should be informed immediately.

Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Moxifloxacin must be discontinued, medical treatment (e.g. treatment for shock) is required.

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Moxifloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Cardiac disorders

Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. 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 drug-associated effects on the QT interval. As the magnitude of QT prolongation may increase with increasing concentrations of the medicine, 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 and QTc prolongation was observed. QT prolongation may lead to an increased risk for ventricular arrhythmias including

torsades de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Moxifloxacin treatment in clinical studies with more than 9000 patients; however certain predisposing conditions may increase the risk for ventricular arrhythmias.

Therefore, treatment with Moxifloxacin should be avoided due to the lack of clinical experience with the medicine in these patient populations:

- 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) antiarrhythmic agents

Moxifloxacin should be used with caution as an additive effect of moxifloxacin on the QT interval cannot be excluded for the following conditions:

- In patients treated concomitantly with medicines that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants
- In patients with ongoing proarrhythmic 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 both may be more susceptible to QTc-prolonging medicines

Hepatobiliary system
Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with Moxifloxacin (see Section 4.8 Undesirable effects). Patients should be advised to contact their doctor immediately prior to continuing treatment if symptoms related to liver failure occur.

Seizures
Seizures may occur with fluoroquinolone therapy. Moxifloxacin should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), which may predispose to seizures or lower the seizure threshold.

Gastrointestinal system
Antibiotic associated colitis has been reported 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 diarrhoeain association with the use of Moxifloxacin. If antibiotic associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

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

Tendinitis and tendon rupture

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with fluoroquinolone therapy including moxifloxacin, even within the first 48 hours of treatment. Cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and patients with solid organ transplants. At the first sign of tendinitis (e.g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued.

Skin and appendages
Fluoroquinolones have been shown to cause photosensitivity reactions in patients. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with Moxifloxacin. In addition, since first marketed there has been no clinical evidence that Moxifloxacin causes photosensitivity reactions. Nevertheless, patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Complicated pelvic inflammatory disease
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, treatment with Moxifloxacin 400 mg tablets is not recommended.

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 Pharmacodynamic properties).

Interaction with tests
Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Moxifloxacin.

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias or weakness have been reported in patients receiving fluoroquinolones including Moxifloxacin. 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 (see Section 4.8 Undesirable effects).

Psychiatric reactions
Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases, depression or psychotic reactions have

progressed to suicidal thoughts and self-injurious behavior such as suicide attempts (see Section 4.8 Undesirable effects). 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 a history of psychiatric disease.

Genital tract infections
Because of the widespread and rising prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* infections, monotherapy with moxifloxacin should be avoided in patients with pelvic inflammatory disease, unless fluoroquinolone- resistant *N. gonorrhoeae* can be excluded. If fluoroquinolone-resistant *N. gonorrhoeae* cannot be excluded, the addition of an appropriate antibiotic which is regularly active against *N. gonorrhoeae* (e.g. a cephalosporin) to empirical moxifloxacin therapy, should be considered.

Dysglycaemia
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia, have been reported with Moxifloxacin. In Moxifloxacin- treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemia agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see Section 4.8 Undesirable effects).

Aortic aneurysm and dissection
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.
Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre- existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Information about excipients
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load of the solution for infusion should be taken into account.

4.5 Interaction with other medicinal products and other forms of interaction

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

Antacids, Minerals and Multi-vitamins
Concomitant ingestion of Moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of moxifloxacin after oral administration

due to formation of chelate complexes with the multi-valent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral medicines (e.g. didanosine), and other preparations containing magnesium or aluminium, sucralfate and agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral moxifloxacin dose.

Ranitidine
The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin. Absorption parameters (Cmax, tmax, AUC) were comparable indicating absence of an influence of gastric pH on moxifloxacin uptake from the GI-tract.

Calcium Supplements
When given with high dose calcium supplements, only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Theophylline
In accordance with *in vitro* data, no influence of moxifloxacin on theophylline pharmacokinetics and *vice versa* at steady state was detected in humans, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes.

Warfarin
No interaction during concomitant treatment with warfarin on pharmacokinetics, prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalised Ratio): Cases of increased anticoagulant activity have been reported in patients receiving anticoagulants concurrently with antibiotics, including Moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between Moxifloxacin and warfarin was not demonstrated in clinical trials, 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
No clinically relevant interaction was seen between glibenclamide and Moxifloxacin.

Itraconazole
Exposure (AUC) to itraconazole was only marginally altered under concomitant Moxifloxacin treatment. Pharmacokinetics of moxifloxacin were 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 not significantly influenced by moxifloxacin and *vice versa*. After repeated dosing in healthy volunteers moxifloxacin increased Cmax of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine
Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased Cmax (17%).

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

Probenecid
No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion.

Charcoal
Concomitant dosing of charcoal and 400 mg oral Moxifloxacin reduced the systemic availability of the medicine by more than 80% by preventing absorption *in vivo*. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous medicine administration carbo medicinalis only slightly reduces systemic exposure (approximately 20%).

Food and Dairy Products
Absorption of moxifloxacin was not altered by food intake (including dairy products). Moxifloxacin can be taken independently from food intake.

4.6 Fertility, pregnancy, and lactation

Pregnancy
The safe use of Moxifloxacin in human pregnancy has not been established. Reversible joint injuries are described in children receivingsome fluoroquinolones, however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown.

Consequently, the use of Moxifloxacin during pregnancy is contraindicated.

Breastfeeding
As with other fluoroquinolones, moxifloxacin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There

are no data available in lactating or nursing women. Therefore, the use of Moxifloxacin in nursing mothers is contraindicated.

Fertility
No data available.

4.7 Effects on ability to drive and use machines.

Fluoroquinolones, including moxifloxacin, may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see Section 4.8 Undesirable effects).

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential [IV/oral]/IV only administration) sorted by CIOMS III categories of frequency (overall n = 17,951, including n = 4,583 from sequential/intravenous therapy studies; status: May 2010) are listed below. ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

ADRs derived from post-marketing reports by the Innovator Moxifloxacin (status: May 2010) are printed in ***bold italic***.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1000 to < 1/100
Rare ≥ 1/10000 to < 1/1000 Very rare < 1/10000

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leukopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged / INR increased	Thromboplastin level abnormal	Prothrombin level increased / INR decreased Prothrombin level / INR abnormal

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Immune System Disorders		Allergic reaction Pruritus Rash Urticaria Blood eosinophilia	Anaphylactic / anaphylactoid reaction Allergic oedema / angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic / anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidemia	Hyperglycaemia Hyperuricaemia	Hypoglycaemia
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts or suicide attempts) Hallucinations	Depersonalisation Psychotic reactions (potentially culminating in self- injurious behaviour, such as suicidal ideation/thoughts or suicide attempts)
Nervous System Disorders	Headache Dizziness	Par- and Dysesthesia 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; in very rare cases leading to fall with injuries, esp. in elderly) Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Eye Disorders		Visual disturbances (esp. in the course of CNS reactions)		Transient loss of vision (esp. in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes * Cardiac arrest * * (esp. in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia)
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea (incl. asthmatic conditions)		
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
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)
Skin and Subcutaneous Tissue Disorders				Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis 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
Renal and Urinary Disorders		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	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

In isolated instances, some serious adverse drug reactions may be long-lasting (>30 days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oralsequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Ventricular tachyarrhythmias, hypotension, oedema, vasodilatation,antibiotic associated colitis (in very rare cases associated with life threatening complications), seizures of various clinical manifestations (including grand mal convulsions), hallucination, renal impairment and renal failure (due to dehydration, especially inelderly with pre-existing renal disorders).

Reporting of 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 via the Pharmacy and Poisons Board Pharmacovigilance Electronic Reporting System (PvERS) at https://pv.pharmacyboardkenya.org

4.9 Overdose

Only limited data on overdose are available. Single doses of up to 1200 mg and multiple doses of 600 mg moxifloxacin over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care including ECG measurements should be instituted as dictated by the patient's clinical status.

The use of charcoal early after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of overdosage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Quinolone antibacterials, fluoroquinolones ATC Code: J01MA14

Mechanism of Action

Moxifloxacin is an 8-methoxy-fluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative organisms, anaerobes, acid-fast bacteria and atypicals e.g. *Chlamydia* spp., *Mycoplasma* spp. and *Legionella* spp.

The bactericidal action results from the interference with topoisomerase II and IV. Topoisomerases are essential enzymes that control DNA topology and assist in DNA replication, repair and transcription.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations.

Moxifloxacin is effective against β-lactam and macrolide resistant bacteria. Studies in animal models of infection have demonstrated high *in vivo* activity.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability amounts to approximately 91%.

Pharmacokinetics are linear in the range of 50 – 1200 mg single dose and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/L are reached within 0.5 – 4 h post application. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3.2 and 0.6 mg/L, respectively.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of fluoroquinolones, this effect is clinically not relevant. Therefore, Moxifloxacin can be administered independently from meals.

After a single 400 mg intravenous 1 hour infusion, peak concentrations of approximately 4.1 mg/L were reached in the plasma at the end of infusion which corresponds to a mean increase of approximately 26% relative to the oral application. Exposure to medicine in terms of AUC at a value of approximately 39 mg.h/L is only slightly higher compared to the exposure after oral administration (35 mg.h/L) in accordance with the absolute bioavailability of approximately 91%.

Following multiple intravenous dosing (1 hour infusion), peak and trough plasma concentrations at steady state (400 mg once daily) were between 4.1 to 5.9 mg/L and 0.43 to 0.84 mg/L, respectively. At steady-state, the exposure to medicine within the dosing interval is approximately 30% higher than after the first dose. In patients, mean steady state concentrations of 4.4 mg/L were observed at the end of a 1 hour infusion.

Distribution

Moxifloxacin is distributed very rapidly to extravascular spaces. Exposure to medicine in terms of AUC (AUCnorm = 6 kg.h/L) is high with a volume of distribution at steady state (Vss) of approximately 2 L/kg. In saliva, peak concentrations higher than those of plasma may be reached. In in vitro and ex vivo experiments over a range of 0.02 to 2 mg/L, a protein binding of approximately 45% independent from the concentration of the medicine was determined. Moxifloxacin is

mainly bound to serum albumin. Due to this low value high free peak concentrations > 10 x MIC are observed.

Moxifloxacin reaches high concentrations in tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polypi) and inflamed lesions (cantharide blister fluid) where total concentrations exceeding those of the plasma concentrations are reached. High free medicine concentrations are measured in interstitial body water (saliva, intramuscular, subcutaneous). In addition, high medicine concentrations were detected in abdominal tissues and fluids and female genital tract.

Peak concentrations of moxifloxacin found in human tissues following oral (upper panel) and intravenous (lower panel) administration of a 400 mg single dose (geometric mean)

Tissue	**Concentration (p.o.)**	**Site: Plasma ratio (p.o.)**
Plasma	3.1mg/L	--
Saliva	3.6 mg/L	0.75 - 1.3
Blister fluid	1.6 mg/L[1]	1.71
Bronchial mucosa	5.4mg/kg	1.7 - 2.1
Alveolar Macrophages	56.7 mg/kg	18.6 - 70.0
Epithelial lining fluid	20.7 mg/L	5 - 7
Maxillary sinus	7.5 mg/kg	2.0
Ethmoid sinus	8.2 mg/kg	2.1
Nasal Polyps	9.1 mg/kg	2.6
Interstitial fluid	1.0 mg/L[2]	0.8 - 1.4[2,3]
Tissue	**Concentration (i.v.)**	**Site: Plasma ratio (i.v.)**
Plasma	4.1 mg/L	--
Saliva	5.0 mg/L	0.82 – 1.37
Blister fluid	1.75mg/L[1]	1.71
Interstitial fluid	1.0 mg/L[2]	0.8 - 2.5[2,3]
Abdominal tissue[4]	7.03 mg/L	1.56
Abdominal exudate[5]	3.32 mg/L	1.45
Abscess fluid[6]	1.94 mg/L	0.74
Female genital tract[4]	10.2 mg/L	1.72

[1] 10 h after administration
[2] unbound concentration
[3] from 3 h up to 36 h post dose
[4] at the end of infusion
[5] 2 hours after administration
[6] 3 h after administration

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

Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged medicine as well as in the form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans. Both are microbiologically inactive. Metabolic pharmacokinetic interactions with other medicines undergoing Phase I biotransformation involving Cytochrome P450 enzymes were not observed in *in vitro* or in clinical Phase I studies.

Independent from the route of administration, the metabolites M1 and M2 are found in the plasma at concentrations lower than the parent medicine. Pre-clinical investigations adequately covered both metabolites, thus excluding potential implications with respect to safety and tolerability.

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. Renal clearance amounted to about 24 – 53 mL/min suggesting partial tubular reabsorption of the medicine from the kidneys. Concomitant administration of ranitidine and probenecid did not alter renal clearance of the medicine (see also table below).

Mass balance of the mother compound and Phase II metabolites of moxifloxacin yielded an almost complete recovery of approximately 96% – 98% independentfrom the route of administration with no indication of oxidative metabolism. A detailed overview of the mass balance according to elimination pathways (renal vs. non- renal, metabolic vs. non-metabolic) and mode of application is given in the table below.

Recovery of a 400 mg single dose (arithmetic mean □ standard deviation (SD))

	Moxifloxacin	**Sulfo-compound (M1)**	**Glucuronide (M2)**	□
Urine p.o.	19.4 □1.2	2.5 □0.6	13.6 □2.8	35.4 □1.8
Faeces p.o.	25.4 □3.1	35.5 □3.2	-	60.9 □5.1
□p.o. (n=6)	44.8 □3.3	37.9 □3.6	13.6 □2.8	96.3 □4.3
Urine i.v.	21.9 □3.6	2.5 □0.9	13.8 □2.0	38.1 □2.1
Faeces i.v.	25.9 □4.3	34.4 □5.6	-	60.2 □9.2
□i.v. (n=5)	47.8 □7.2	36.8 □5.9	13.8 □2.0	98.4 □10.5

Resistance

Resistance mechanisms which inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. There is no cross-resistance between moxifloxacin and these agents. Plasmid-mediated resistance has not been observed to date.

It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, a mechanism of fluoroquinolone resistance.

In vitro studies have demonstrated that resistance to moxifloxacin develops slowly by multiple step mutations. A very low overall frequency of resistance was demonstrated (10-7 – 10-10). Serial exposure of organisms to sub-MIC concentrations of moxifloxacin showed only a small increase in MIC values.

Cross-resistance among fluoroquinolones has been observed. However, some gram-positive and anaerobic organisms resistant to other fluoroquinolones are susceptible to moxifloxacin.

Effect on the Intestinal Flora in Humans

In two volunteer studies, the following changes in the intestinal flora were seen following oral dosing with moxifloxacin. *E. coli, Bacillus* spp*., Bacteroides vulgatus*, *Enterococci*, and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium, Eubacterium*, and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

In vitro Susceptibility Data

Susceptible	Intermediate	Resistant
Gram-positive bacteria		
Gardnerella vaginalis		
*Streptococcus pneumoniae** incl. multi- drug resistant *S. pneumoniae* strains [MDRSP] incl. strains known as PRSP (Penicillin-resistant *S. pneumoniae*), andstrains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 µg/mL, 2nd generation cepahalosporins(e.g. cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.		
Streptococcus pyogenes (group A)*		
Streptococcus milleri group (*S. anginosus*, S. constellatus*, and S.intermedius**)		
Streptococcus viridans group (*S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus, S.constellatus)*		
Streptococcus agalactiae		
Streptococcus dysgalactiae		
Staphylococcus aureus (methicillinsusceptible strains)*		*Staphylococcus aureus* (methicillin/ofloxacin resistant strains)+
*Coagulase negative Staphylococci (S. cohnii, S. epidermidis, S. haemolyticus, S.hominis, S. saprophyticus, S. simulans)*methicillin susceptible strains		Coagulase negative Staphylococci (*S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans)* methicillinresistant strains

	*Enterococcus faecalis** *(*Vancomycin, Gentamycin susceptible strains only)	
	*Enterococcus avium**	
	*Enterococcus faecium**	

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

+ Moxifloxacin is not recommended for the treatment of methicillin resistant *S. aureus* (MRSA) infections. In case ofa suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial ag ent should be started.

Susceptible	Intermediate	Resistant
Gram-negative bacteria		
Haemophilus influenzae (incl. □ lactamase negative and positive strains)*		
*Haemophilus parainfluenzae**		
Moraxella catarrhalis (incl. □ lactamase negative and positive strains)*		
Bordetella pertussis		
Legionella pneumophila	*Escherichia coli**	
Acinetobacter baumanii	*Klebsiella pneumoniae**	
	Klebsiella oxytoca	
	*Citrobacter freundii**	
	Enterobacter species (*E. aerogenes, E. intermedius, E. sakazaki)*	
	*Enterobacter cloacae**	
	Pantoea agglomerans	
		Pseudomonas aeruginosa
	Pseudomonas fluorescens	
	Burkholderia cepacia	
	Stenotrophomonas maltophilia	
	*Proteus mirabilis**	
Proteus vulgaris		
	Morganella morganii	
	Providencia species (*P. rettgeri, P. stuartii)*	
	*Neisseria gonorrhoea***	

*/** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Susceptible	Intermediate	Resistant
Anaerobes		

	Bacteroides spp. *(B. fragilis*, B. distasoni*, B. thetaiotaomicron*, B. ovatus*, B. uniformis*, B. vulgaris*)*	
Fusobacterium spp.		
	*Peptostreptococcus spp.**	
Porphyromonas spp.		
Prevotella spp.		
Propionibacterium spp.		
	*Clostridium sp**	

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Susceptible	Intermediate	Resistant
Atypicals		
*Chlamydia pneumoniae**		
*Chlamydia trachomatis***		
*Mycoplasma pneumoniae**		
Mycoplasma hominis		
Mycoplasma genitalum		
Coxiella burnetti		

*/** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections. The above information is provided as a guide on the probability of an organism being susceptible to moxifloxacin.

Comparison of PK/PD surrogates for intravenous and oral administration of a 400 mg Moxifloxacin single dose.
In patients requiring hospitalisation, AUC/MIC90 parameters greater than 125 and Cmax / MIC90 of 8 – 10 is predictive for clinical cure (Schentag). In outpatients, these surrogate parameters are generally smaller, i.e. AUC/MIC90 greater than 30 – 40 (Dudley and Ambrose).

The following table provides the respective PK/PD surrogates for intravenous and oral administration of 400 mg moxifloxacin calculated from single dose data:

Mode of administration	**Intravenous**		**oral**	
Parameter (median)	AUIC [h]	C_{max}/MIC_{90} [a)]	AUIC [h]	C_{max}/MIC_{90}
MIC_{90} 0.125 mg/L	313	32.5	279	23.6
MIC_{90} 0.25 mg/L	156	16.2	140	11.8
MIC_{90} 0.5 mg/L	78	8.1	70	5.9

[a)] 1h infusion

Geriatric Patients
Pharmacokinetics of moxifloxacin are not affected by age.

Gender
There was a 33% difference in the pharmacokinetics (AUC, Cmax) of moxifloxacin between male and female subjects. Absorption was unaffected by gender. These differences in the AUC and Cmax were attributable to the differences in body weight rather than gender. They are not considered as clinically relevant.

Ethnic Differences
Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Paediatric population
Pharmacokinetics of moxifloxacin were not studied in paediatric patients.

Patients with Renal Impairment
The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

Patients with Hepatic impairment
Plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Section 4.4 Special Warnings and Precautions for Use, in patients with liver cirrhosis).

5.3 Preclinical safety data

As for other fluoroquinolones, the major toxicological target organs for moxifloxacin were the haemopoietic system (hypocellularity of the bone marrow in dogs and monkeys), the central nervous system (convulsions in monkeys) and the liver (raised liver enzymes, single cell necrosis in rats, dogs and monkeys). These changes were commonly seen only after treatment with high doses of moxifloxacin or after prolonged treatment.

In a local tolerability study performed in dogs, no signs of local intolerability were seen when moxifloxacin was administered intravenously. After intra-arterial injection, inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

Carcinogenicity, Mutagenicity
Although conventional long-term studies to determine the carcinogenic potential of moxifloxacin have not been performed, the medicine has been subject to a range of *in vitro* and *in vivo* genotoxicity tests. In addition, an accelerated bioassay for human carcinogenesis (initiation /promotion assay) was performed in rats. Negative results were obtained in 4 strains of the Ames test, in the HPRT mutation assay in Chinese hamster ovary cells and in the UDS assay in rat primary hepatocytes. As with other fluoroquinolones, the Ames test with TA 102 was positive and the *in vitro* test in the Chinese hamster v79 cells showed chromosomal abnormalities at high concentrations (300 □g/mL). However, the *in vivo* micronucleus assay in the mouse was negative. An additional *in vivo* assay, the dominant lethal assay in the mouse, was negative as

well. It is concluded that the negative *in vivo* results adequately reflect the *in vivo* situation in terms of genotoxicity. No evidence of carcinogenicity was found in an initiation/promotion assay in rats.

Phototoxicity

Moxifloxacin is very photostable and has a very low potential for photogenotoxicity. *In vitro* and in animal models moxifloxacin seems to show less potency to induce phototoxicity and photogenotoxocity than other fluoroquinolones. Some fluoroquinolones have been shown to enhance the action of UV-A-induced photocarcinogenicity when administered concurrently to mice exposed to ultraviolet light. No photocarcinogenicity study has been performed with moxifloxacin. The lack of phototoxic potential has been confirmed in a Phase I study in volunteers.

ECG
At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT-interval. Toxicological studies performed in dogs using oral doses of 90 mg/kg leading to plasma concentrations 16 mg/L caused QT-prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50 fold the human dose (> 300 mg/kg), leading to plasma concentrations of 200 mg/L (more than 30 fold the therapeutic level after intravenous administration), reversible, non- fatal ventricular arrhythmias were seen.

Oculotoxicity
Toxicity tests in rats and monkeys (repeated dosing up to six months) revealed no indication regarding an oculotoxic risk. 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.

Arthrotoxicity
Fluoroquinolones are known to cause lesions in the cartilage of the major diarthodial joints in immature animals. The lowest oral dose of moxifloxacin causing joint toxicity in juvenile dogs was four times maximum recommended therapeutic dose (400 mg/50 kg person) on a mg/kg basis, with plasma concentrations two to three times higher than those at the recommended therapeutic dose.

Reprotoxicity
Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (per os and i.v.) and monkeys (per os) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. Skeletal malformations were observed in rabbits that had been treated with an intravenous dose of 20 mg/kg. This study result is consistent with the known effects of fluoroquinolones on skeletal development (see Section 4.5 Interaction with other medicines and other forms of interaction and Section 4.6 Fertility, pregnancy and lactation). There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring were observed at

doses which were 63 times the maximum recommended dose on a mg/kg basis, with plasma concentrations in the range of the human therapeutic dose.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride
Hydrochloric Acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

The following infusions were found to be incompatible with Moxifloxacin solution for infusion:

- Sodium Chloride 10%
- Sodium Chloride 20%
- Sodium Hydrogen Carbonate 4.2%
- Sodium Hydrogen Carbonate 8.4%

6.3 Shelf life

2 years.

6.4 Special precautions for storage:

Store below 30°C. Do not refrigerate or freeze.
The product should be used immediately after opening.

6.5 Nature and contents of container

Mofloxine® 1.6mg/ml Solution for Infusion: Each 1ml contains Moxifloxacin 1.6 mg in packs of 250ml Bag.
Mofloxine is packed in 300ml Polyolefin bag plugged with plug for bag and then in (160*310) mm Aluminum pouch.

6.6 Special precautions for disposal and other handling:

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder and Manufacturing site:
MS Pharma
Amman, Sahab- street no.6,
Building no.356
Jordan.
Tel: 06-4020680
Fax: 06-4020681
06-4162905

Local Technical Representative:
Generics Africa Ltd.

Aqua office Suites, 5th Floor, Muranga road,
P.O Box 69652-00400,
Nairobi, Kenya.

8. Marketing authorization number
CTD7023

9. Date of first registration
03-03-2024

10. Date of revision of the text:
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