1 PRODUCT NAME

Moxifloxacin Kabi 400 mg/250 mL intravenous infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Moxifloxacin (as hydrochloride) 400 mg/250 mL
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intravenous infusion

Moxifloxacin Kabi is available in ready-to-use 250 mL (containing 400 mg moxifloxacin) free*flex*® bags or Kabi**Pac**® infusion bottles, as a sterile, preservative-free aqueous solution of moxifloxacin hydrochloride with pH ranging from 5.0 to 6.0. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Moxifloxacin Kabi Injection 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 Dose and method of administration

Dose

The recommended dose for Moxifloxacin is 400mg once daily (250 mL solution for infusion) for the above-mentioned indications and should not be exceeded.

Duration of Treatment

The duration of treatment should be determined by the severity of the indication or clinical response. The following are general recommendations:

Solution for Infusion

Bronchitis:	acute exacerbation of chronic bronchitis 5 days
Pneumonia:	community acquired pneumonia (intravenous followed by oral therapy), 7- 14 days
Sinusitis:	acute sinusitis, 7 days

Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 7 – 21 days

Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 5 – 14 days.

Moxifloxacin can be administered intravenously for the entire treatment duration. Alternatively, therapy may be initial intravenous administration, followed by oral administration of filmcoated tablets * when clinically indicated.

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

Film-coated tablet *

Bronchitis: acute exacerbation of chronic bronchitis, 5 days

Pneumonia: community acquired pneumonia, 10 days

Sinusitis: acute sinusitis, 7 days

Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 7 – 21 days

Uncomplicated pelvic inflammatory disease: 14 days

Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 5 – 14 days

**Moxifloxacin tablets are unavailable in this brand, however are available in other brands. Where the tablet formulation is clinically indicated, moxifloxacin tablets from other suppliers should be used.*

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

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric population

The use of moxifloxacin in children is not recommended (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of moxifloxacin in this patient group is not recommended (see section 4.4 Special warnings and precautions for use for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

Method of administration

Moxifloxacin Kabi should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal or subcutaneous administration.

Moxifloxacin Kabi should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Parenteral medicine products should be inspected visually for particulate matter and discolouration prior to the administration. Only clear solution free from particles should be used.

Moxifloxacin Kabi is for single use in one patient only. Discard any residue. It contains no antimicrobial preservatives. Only clear solutions are to be used. It is to be used immediately after the bag or bottle is opened.

Refer to Section 6.6 for information on compatible infusion solutions.

4.3 Contraindications

Known hypersensitivity to any component of Moxifloxacin Kabi or to any other quinolone or any of the excipients.
Pregnancy and lactation.
Patients below 18 years of age

Refer to Sections 4.6 for information on Fertility, Pregnancy and Lactation and 6.2 for information on incompatible solutions for infusions.

4.4 Special warnings and precautions for use

[Oral moxifloxacin is unavailable in this brand, however is available in other brands. Precaution information relating to the oral formulation of moxifloxacin is also included in the following sub-sections for completion and for information of the prescribers].

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.

QT prolongation and cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5,000 patients treated with oral moxifloxacin including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive moxifloxacin. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore moxifloxacin should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Moxifloxacin should be used with caution in patients with ongoing pro-arrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Use with caution in patients with liver cirrhosis as pre-existing QT prolongation cannot be excluded

Gastrointestinal System

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inhibiting peristalsis are contraindicated in this situation.

Effects on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Moxifloxacin Kabi should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS

Seizures may occur with quinolone 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), that may predispose them to seizures or lower the seizure threshold.

Myasthenia gravis

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

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. Moxifloxacin Kabi should be discontinued in patients experiencing symptoms of neuropathy including pain, burning, tingling, numbness and/or weakness in order to prevent the development of an irreversible condition (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 behaviour such as suicide attempts (see section 4.8 Undesirable effects). In the event that the patient develops these reactions, Moxifloxacin Kabi 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.

Vision disorders

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

Paediatric population

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, moxifloxacin should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of moxifloxacin in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8 Undesirable effects, Post-marketing adverse event reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

Photosensitivity potential

Phototoxicity has been reported with other quinolones. 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.

Hypersensitivity reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Moxifloxacin Kabi should be discontinued and appropriate therapy commenced in these cases.

Skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see section 4.8 Undesirable effects, Post-marketing adverse event reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis, there are no data demonstrating the efficacy and safety of treatment with moxifloxacin.

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 hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8 Undesirable effects).

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

Sodium content of solution for infusion

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. The sodium content of the solution for infusion (250 mL) is 54.4 mmol.

Other

Moxifloxacin 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 5.2 Pharmacokinetic properties, Microbiology).

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.

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 has to be discontinued, medical treatment (e.g. treatment for shock) is required.

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.

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 for patients

To assure safe and effective use of Moxifloxacin Kabi, the following information and instruction should be communicated to the patient when appropriate.

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light- headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.

- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

4.5 Interaction with other medicines and other forms of interaction

[Oral moxifloxacin is unavailable in this brand however is available in other brands. Information relating to interactions with other medicines obtained using oral moxifloxacin is also included in the following sub-sections for completion and for information of the prescribers].

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.

See section 4.3 Contraindications and section 4.4 Special warnings and precautions for use for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of moxifloxacin should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of moxifloxacin should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

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 drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal 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.

Warfarin

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

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral 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 C_{max} 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 C_{max} (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%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

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. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Charcoal

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

4.6 Fertility, pregnancy and lactation

Pregnancy (Category B3)

[Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans].

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 quinolones on skeletal development (see Interaction with Other Medicinal Products and Other Forms of Interaction, 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 was 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.

Breast-feeding

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking moxifloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats.

Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

4.7 Effects on ability to drive and use machines

Moxifloxacin may cause dizziness and light headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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

[Oral moxifloxacin is unavailable in this brand however is available in other brands. Information relating to adverse effects obtained using oral moxifloxacin is also included in the following sub-sections for completion and for information of the prescribers].

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 (status: May 2010) are printed in **bold italic**.

Within each frequency grouping, the ADRs 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 Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis 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		Hyperlipidaemia	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)**

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Nervous System Disorders	Headache Dizziness	Par-/Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder 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
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially 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 (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
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)	
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/oral sequentially 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 in elderly with pre-existing renal disorders).

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 https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

[Oral moxifloxacin is unavailable in this brand however is available in other brands. Pharmacokinetic information obtained using oral moxifloxacin is also included in the following sub-sections for completion and for information of the prescribers].

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	Quinolone antibacterials, fluoroquinolones
ATC codes:	J01MA14, S01AE07

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone 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 and Bioavailability

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 400mg 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 quinolones, this effect is clinically not relevant. Therefore, moxifloxacin can be administered independently from meals.

After a single 400 mg intravenous 1hour 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 (1hour 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 1hour 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% independent from 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

Special populations

Geriatric
No adjustment of dosage is required in the elderly

Paediatric Population
The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex
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.

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

Renal impairment
The pharmacokinetics of moxifloxacin are not significantly changed by 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.

Hepatic impairment
Moxifloxacin 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 section 4.4 Special warnings and precautions for use for use in Child Pugh C patients).

Microbiology

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

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 quinolones has been observed. However, some gram-positive and anaerobic organisms resistant to other quinolones are susceptible to moxifloxacin.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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*), and strains 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 (methicillin susceptible 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)* methicillin
	*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 of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started.

Susceptible	Intermediate	Resistant
Gram-negative bacteria		
Haemophilus influenzae (incl. β lactamase negative and positive strains)*		
*Haemophilus parainfluenzae**		
Moraxella catarrhalis (incl. β lactamase negative and positive strains)*		
Bordetella pertussis		
Legionella pneumophilia	*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		
*Legionella pneumophila**		
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 400mg 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

5.3 Preclinical safety data

As for other quinolones 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 and genotoxicity

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 quinolones 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 quinolones. Some quinolones 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

Quinolones 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium acetate trihydrate
- Disodium sulfate
- Water for Injections
- Sulfuric acid (pH adjustment).

6.2 Incompatibilities

The following solutions for infusion must not be administered with Moxifloxacin Kabi –

- Sodium chloride 10%
- Sodium chloride 20%
- Sodium hydrogen carbonate 4.2%
- Sodium hydrogen carbonate 8.4%.

6.3 Shelf life

free*flex*® bag and Kabi**Pac**® bottle

36 months

6.4 Special precautions for storage

free*flex*® bag and Kabi**Pac**® bottle

- Store solution between 15°C–25°C.
- Do not store below 15°C as solution will precipitate.
- Do not refrigerate or freeze solution.

Kabi**Pac**® bottle

Keep in outer carton, to protect from light.

6.5 Nature and contents of container

free*flex*® bag

Polyolefine bags with an administration port (infusion port) and addition port (injection port) consisting of a polypropylene housing and an aluminium overpouch.
Available in *packs of 1, 10, 20, 25 and 40 bags.

Kabi**Pac**® bottle

Low-density polyethylene bottles as primary packaging closed with a cap containing a rubber disc to allow insertion of the needle.
Available in *packs of 1, 10, 20, 25 and 40 bottles.

**Not all pack sizes may be marketed.*

6.6 Special precautions for disposal and handling

No special requirements for disposal.

Since only limited data are available on the compatibility of Moxifloxacin Kabi with other intravenous substances, additives or other medications should not be added to Moxifloxacin Kabi or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Moxifloxacin Kabi with an infusion solution compatible with Moxifloxacin Kabi as well as with other drug(s) administered via this common line.

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.

Compatible solutions for infusion
Moxifloxacin Kabi is compatible with the following intravenous solutions. The mixture ratio of Moxifloxacin Kabi 400 mg/250 ml with each solution was 1:1.

Sodium Chloride 0.9%
Dextrose 5%
Dextrose 10%
Water for Injections
Ringers Solution
Ringers Lactate Solution

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Moxifloxacin Kabi.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Fresenius Kabi New Zealand Limited
c/o GNZCC , HSBC Tower, Level 14, 188 Quay Street,
Auckland 1010, New Zealand.
Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
1st November 2018

10 DATE OF REVISION OF THE TEXT

8 September 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
n.a	New Data Sheet
4.4	Alignment with NZ innovator: Addition of precaution regarding aortic aneurysm and dissection. Addition of risk factors for tendon disorders, and addition of characteristics for tendinitis and tendon rupture. Statement regarding risk of seizures updated. Multiple titles provided for precautions
4.8	Addition of information on potential long-lasting and disabling ADRs