AVELOX® Solution for Infusion

Prescription use only

1. NAME OF THE MEDICINAL PRODUCT

Avelox 400 mg solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 bottle or bag contains 250 mL solution for infusion containing 400 mg moxifloxacin (as hydrochloride)

3. PHARMACEUTICAL FORM

Solution for infusion

250 mL polyolefine flexible bag filled with minimum 250 mL clear, yellow solution

250 mL glass bottle with clear, yellow solution filled with minimum 250 mL

4. CLINICAL PARTICULARS

4.1 Indications

Avelox 400 mg solution for infusion is indicated for the treatment of the following bacterial infection caused by susceptible strains:

- Community acquired pneumonia caused by *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae* or *Moraxella catarrhalis*.
- Complicated skin and skin structure infections caused by methicillin-susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* or *Enterobacter cloacae.*

For full list of susceptible strains, please refer to Pharmacodynamic Properties.

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

4.2 Dosage and method of administration

4.2.1 Method of administration

Solution for Infusion:
The infusion solution should be infused intravenously over 60 minutes.

The solution for infusion can be administered directly or via a T-tube together with compatible infusion solutions.

The following coinfusions were found to form stable mixtures over a period of 24 hours at room temperature with Avelox infusion solution, and can therefore be considered as compatible with Avelox solution for infusion:

Water for Injections
Sodium Chloride 0.9%
Sodium Chloride 1 molar
Glucose 5%
Glucose 10%
Glucose 40%
Xylitol 20%
Ringer's Solution
Lactated Ringer's Solution

If Avelox infusion solution is to be given with another drug, each drug should be given separately (see "Pharmaceutical Particulars, Incompatibilities").

Only clear solutions are to be used.

4.2.2 Dosage regimen

Dose (adults):

The recommended dose for Avelox is 400 mg once-daily (250 mL solution for infusion) for the above-mentioned indication 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 general recommendations for the treatment of upper and lower respiratory tract infections and skin infections are made:

Therapy may be initial intravenous administration, followed by oral administration of film-coated tablets. When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox Tablets when clinically indicated at the discretion of the physician.

Pneumonia: community acquired pneumonia: The recommended total treatment duration for sequential administration (intravenous followed by oral) is 7-14 days.

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

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

Avelox 400 mg film-coated tablets and Avelox 400 mg solution for infusion have been studied in clinical trials for up to 21 days (in complicated skin and skin structure infections).

4.2.3 Missed dose
If a dose is missed it should be taken anytime but not later than 8 hours prior tothe next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose.. Double doses should not be taken to compensate for a missed dose.

4.2.4 Additional information on special populations

4.2.4.1 Children and adolescents
Efficacy and safety of Avelox in children and adolescents have not been established (see- "Contraindications").

4.2.4.2 Geriatric patients
No adjustment of dosage is required in elderly.

4.2.4.3 Ethnic differences
No adjustment of dosage is required in ethnic groups.

4.2.4.4 Patients with hepatic impairment
No dosage adjustment is required in patients with mild or moderate impaired liver function. The use of moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C) (see "Special warnings and precautions for use" in Child Pugh C patients).

4.2.4.5 Patients with renal impairment
No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance $\leq$ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

4.3 Contraindications

Known hypersensitivity to moxifloxacin or other quinolones or any of the excipients.

Pregnancy and lactation.

Patients below 18 years of age.

Patients with a history of tendon disease/disorder related to quinolone treatment.

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

- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia

- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

Avelox should not be used concurrently with other drugs that prolong the QT interval (see also "Interactions with other medicaments and other forms of interaction").

Moxifloxacin is contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase >5 fold ULN.

4.4 Special warnings and precautions for use

Hypersensitivity
In some instances, the hypersensitivity and allergic reactions already 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 Avelox has to 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 Avelox (see"Undesirable Effects"). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Cardiac disorders
Avelox 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 drug, the recommended dose and infusion rate (400mg 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 torsade des pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Avelox treatment in clinical studies with more than 9000 patients, however, certain predisposing conditions may increase the risk for ventricular arrhythmias.

<u>Therefore, treatment with Avelox should be avoided due to the lack of clinical experience with the drug in these patient populations:</u>

- In patients with known prolongation of the QT interval
- In patients with uncorrected hypokalemia
- In patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents

<u>Avelox should be used with caution as an additive effect of moxifloxacin on the QT interval cannot be excluded for the following conditions:</u>

- In patients treated concomitantly with drugs 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 ischemia.
- 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 drugs.

Treatment with moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.
Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels.
Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia.

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

Due to limited clinical data the use of moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C).

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

Disabling and potentially irreversible serious adverse reactions
Fluoroquinolones, including Avelox, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions.
Discontinue Avelox immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including Avelox, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

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 antibiotics treatment should be discontinued.

Consult your doctor immediately in order to initiate appropriate treatment (e.g. immobilisation) for the affected tendon. Tendon inflammation and rupture may occur even up to several months after discontinuing quinolone therapy including moxifloxacin

Aortic aneurysm or dissection and heart valve regurgitation/incompetence
Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

Therefore, fluoroquinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in
patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis) or additionally

- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

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

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

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Gastrointestinal system
Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is

suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission.

Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

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

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 Avelox. In addition, since first marketed there has been no clinical evidence, that Avelox causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight. If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Complicated pelvice 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 Avelox 400 mg film-coated 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 “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 Avelox.

Peripheral neuropathy
Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones including Avelox. Symptoms may occur soon after initiation of Avelox and may be irreversible. Avelox should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation.

Psychiatric adverse reactions
Fluoroquinolones, including Avelox, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving Avelox, discontinue Avelox immediately and institute appropriate measures.
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.

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

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

Blood glucose disturbances
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with Avelox. In Avelox-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue Avelox and initiate appropriate therapy Immediately.

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. For sodium chloride content of the solution for infusion see “Qualitative and quantitative composition”.

4.5 Interaction with other medicinal products and other forms of interaction

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

<u>Antacids, minerals and multi-vitamins</u>
Concomitant ingestion of Avelox 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 drugs (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.

<u>Warfarin</u>
No interaction during concomitant treatment with warfarin on pharmacokinetics, 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 anticoagulants concurrently with antibiotics, including

Avelox. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between Avelox 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.

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.

Charcoal
Concomitant dosing of charcoal and 400 mg oral Avelox reduced the systemic availability of the drug 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 drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Food and dairy products
Absorption of moxifloxacin was not altered by food intake (including dairy products). Avelox can be taken independent from food intake.

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

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

4.6 Pregnancy and lactation

4.6.1 Pregnancy
The safe use of Avelox in human pregnancy has not been established. Reversible joint injuries are described in children receiving some 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 Avelox during pregnancy is contraindicated.

4.6.2 Lactation
As with other fluoroquinolones, Avelox 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 is no data available in lactating or nursing women. Therefore, the use of Avelox in nursing mothers is contraindicated.

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 "Undesirable Effects").

4.8 Undesirable effects

4.8.1 Tabulated list of adverse reactions

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential [IV/oral]/intravenous only administration) sorted by CIOMS III categories of frequency (overall n= 17,951, including n 4,583 for 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 diarrhea.
ADRs derived from post marketing reports (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 (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000),
very rare (< 1/10,000).

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Mycotic super-infections				
Blood and the lymphatic system disorders		Anemia Leukopenia(s) Neutropenia Thrombo-cytopenia Thrombo-cythemia 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	Not known
Immune system disorders		Allergic reaction Pruritus Rash Urticaria Blood eosinophilia	Anaphylactic / anaphylactoid reaction Allergic edema / angioedema (incl. laryngeal edema, potentially life threatening)	Anaphylactic / anaphylactoid shock (potentially life threatening)	
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia	
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional liability Depression ***(in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts)*** Hallucinations	Depersonali-zation Psychotic reactions, ***(potentially culminating in self-injurious behavior, 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	Hypoesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo (***in very rare cases leading to fall***	Hyperesthesia	Peripheral neuropathy (that may be irreversible) and polyneuropathy

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare	Not known
			with injuries, esp. in elderly) Seizures of various clinical manifesta-tions (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia		
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 tachy-arrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias ***Torsade de Pointes **** ***Cardiac arrest **** **** (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)***	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare	Not known
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)			
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhea	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)		
Hepato-biliary 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)***	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare	Not known
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 diarrhea 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	Edema		

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, Edema, Antibiotic associated colitis (in very rare cases associated with life threatening complications), Seizures of various clinical manifestations (incl. grand mal convulsions),

Hallucination, Renal impairment and renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)

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.
The use of charcoal early during absorption after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin. After intravenous drug administration, charcoal only slightly reduces systemic exposure (approx. 20%) and is of limited use in case of intravenous overdosing.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones
ATC Code: J01MA 14

5.1.1 Mechanism of action

Moxifloxacin is a 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 eg. *Mycoplasma* spp., *Chlamydia* spp. and *Legionella* spp.

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

5.1.2 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.

Moxifloxacin has been shown to be active against most strains of the following microorganisms , both in vitro and in clinical infections as described in the "Indications" section.

5.1.3 In vitro Susceptibility Data

Susceptible	**Intermediate**	**Resistant**
Gram-positive bacteria		
Gardnerella vaginalis		
*Streptococcus pneumoniae** including multi-drug resistant streptococcus pneumoniae strains [MDRSP] including 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 cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole		
*Streptococcus pyogenes (group A)**		
Streptococcus milleri group (*S. anginosus**, *S. constellatus**, and *S. intermedius**)		

Susceptible	**Intermediate**	**Resistant**
Gram-positive bacteria		
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 resistant strains
	*Enterococcus faecalis** (Vancomycin,Gentamycin, susceptible strains only)	
	*Enterococcus avium**	
	*Enterococcus faecium**	

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

[+] Avelox 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 (including ß lactamase negative and positive strains) *		
Haemophilus parainfluenzae *		

Susceptible	**Intermediate**	**Resistant**
Gram-negative bacteria		
Moraxella catarrhalis (including ß 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	
	*Neisseria gonorrhoea **	
	Providencia species (*P. rettgeri, P. stuartii*)	

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

Susceptible	Intermediate	Resistant
Anaerobes		
	Bacteroides sp (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 burnettii		

*/** 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 Avelox single dose.

In patients requiring hospitalisation AUC/MIC_{90} parameters greater than 125 and C_{max} / MIC_{90} of 8 – 10 is predictive for clinical cure (Schentag). In outpatients these surrogate parameters are generally smaller, i.e. AUC/MIC_{90} 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

5.2 Pharmacokinetic properties

5.2.1 Absorption and bioavailability

Following oral administration moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability amounts to approx. 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 hours postapplication. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively.

Concomitant administration of oral 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, Avelox 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 approx. 26 % relative to the oral application. Exposure to drug 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 and 0.43 to 0.84 mg/L respectively. At steady-state the exposure to drug 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.

5.2.2 Distribution

Moxifloxacin is distributed very rapidly to extravascular spaces. Exposure to drug in terms of AUC (AUC_{norm} = 6 kg*h/l) is high with a volume of distribution at steady state (V_{ss}) 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 drug 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 drug concentrations are measured in interstitial body water (saliva, intramuscular, subcutaneous). In addition, high drug concentrations were detected in abdominal tissues and fluids and female genital tract.

Tissue	**Concentration (p.o.)**		**Site: Plasma ratio (p.o.)**
Plasma	3.1	mg/L	--
Saliva	3.6	mg/L	0.75 -1.3
Blister fluid	1.6[1]	mg/L	1.7[1]
Bronchial mucosa	5.4	mg/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[2]	mg/L	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	1.75[1]	mg/L	1.71
Interstitial fluid	1.0[2]	mg/L	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 drug administration after a single dose of 400 mg moxifloxacin.

5.2.3 Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. Neither in *in vitro* nor in clinical Phase I studies metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving Cytochrome P-450 enzymes were observed.

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

5.2.4 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 drug from the kidneys. Concomitant administration of ranitidine and probenecid did not alter renal clearance of the drug (see 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 ± 4.3
∑ 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

5.2.4.1 Geriatric patients

Pharmacokinetics of moxifloxacin are not affected by age.

5.2.4.2 Gender

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

5.2.4.3 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.

5.2.4.4 Children and adolescents

Pharmacokinetics of moxifloxacin were not studied in pediatric patients.

5.2.4.5 Patients with 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. hemodialysis and continuous ambulatory peritoneal dialysis.

5.2.4.6 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 “Special Warnings and Precautions for use” in Child Pugh C patients).
There is no experience in patients with severe hepatic impairment (Child Pugh C).

5.3 Preclinical safety data

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.

5.3.1 Carcinogenicity, Mutagenicity

Moxifloxacin, like other fluoroquinolones, was genotoxic in vitro tests using bacteria or mammalian cells. Since these effects can be explained by an interaction with the gyrase in bacteria and –at higher concentrations – by an interaction with the topoisomerase II in mammalian cells, a threshold concentration for genotoxicity can be assumed. In in-vivo tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

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.

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 “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.

6. PHARMACEUTICAL PARTICULARS

List of excipients:

Solution for infusion: Sodium chloride Ph.Eur., USP, Ph.Jap., hydrochloric acid 1N, sodium hydroxide solution 2N, water for injection Ph.Eur., USP, Ph.Jap.

Incompatibilities:

Solution for infusion:

The following coinfusions were found to be incompatible with Avelox infusion solution:
Sodium Chloride 10%
Sodium Chloride 20%
Sodium Hydrogen Carbonate 4.2%
Sodium Hydrogen Carbonate 8.4%

Special precautions for use include storage recommendations

Store between 15°C to 30°C
At temperatures below 15°C, precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator.

The product should be inspected visually for particles prior to administration. Only clear solution free form should be used.

Store in the original container.

Presentation

12 x 250ml polyolefine-bags
1 x 250ml glass vial

Not all presentations may be available locally

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

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Product Owner:
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