SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Avelox 400 mg/250 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 bottle of 250 ml contains 400 mg moxifloxacin (as hydrochloride).
1 ml contains 1.6 mg moxifloxacin (as hydrochloride).

Excipient with known effect: 250 ml of solution for infusion contains 787 mg (34 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Avelox is indicated for the treatment of:
- Community acquired pneumonia (CAP)
- Complicated skin and skin structure infections (cSSSI)

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

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

4.2 Posology and method of administration

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

Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400 mg tablets, when clinically indicated.
In clinical studies most patients switched to oral therapy within 4 days (CAP) or 6 days (cSSSI). The recommended total duration of intravenous and oral treatment is 7 – 14 days for CAP and 7 – 21 days for cSSSI.

Renal/hepatic impairment
No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis (see section 5.2 for more details).
There is insufficient data in patients with impaired liver function (see section 4.3).

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

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

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

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

4.3 Contraindications

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

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin is therefore contraindicated in patients with:
- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

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

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

4.4 Special warnings and precautions for use

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

The benefit of moxifloxacin treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section.

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

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

Treatment with moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.
Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischaemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. See also sections 4.3 and 4.5.

Moxifloxacin should be used with caution in patients who are taking medications that can reduce potassium levels. See also sections 4.3 and 4.5.
Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia. See also section 4.3.
Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as moxifloxacin and therefore special caution is required.

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

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

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and Acute Generalised Exanthematous Pustulosis (AGEP), which could be life-threatening or fatal, have been reported with moxifloxacin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, moxifloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or AGEP with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.

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

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Moxifloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

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

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

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

Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment (see sections 4.3 and 4.8). The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

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 aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. 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.

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

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Dysglycemia
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with moxifloxacin (see section 4.8). In moxifloxacin-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

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

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

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

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

Interference with biological tests
Moxifloxacin therapy may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving moxifloxacin.

Patients with MRSA infections
Moxifloxacin is not recommended for the treatment of MRSA infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see section 5.1).

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

Information about excipients
This medicinal product contains 787 mg (approximately 34 mmol) sodium per bottle with 250 ml solution for infusion, equivalent to 39.35 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products
An additive effect on QT interval prolongation of moxifloxacin and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore, co-administration of moxifloxacin with any of the following medicinal products is contraindicated (see also section 4.3):
- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)

- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

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

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

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

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

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

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

Interaction with food
Moxifloxacin has no clinically relevant interaction with food including dairy products.

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1,000 to < 1/100)
- rare (≥ 1/10,000 to < 1/1,000)
- very rare (< 1/10,000)
- not known (cannot be estimated from the available data)

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis				
Blood and lymphatic system disorders		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged/INR increased		Prothrombin level increased/INR decreased Agranulo-cytosis Pancytopenia	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Immune system disorders		Allergic reaction (see section 4.4)	Anaphylaxis incl. very rarely life-threatening shock (see section 4.4) Allergic oedema/ angiooedema (incl. laryngeal oedema, potentially life-threatening, see section 4.4)		
Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia Hypoglycaemic coma	
Psychiatric disorders*		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression (in very rare cases potentially culminating in self- injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4) Hallucination Delirium	Depersonalization Psychotic reactions (potentially culminating in self- injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4)	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Nervous system disorders*	Headache Dizziness	Par- and Dysaesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions (see section 4.4) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia	
Eye disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)	Photophobia	Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7) Uveitis and bilateral acute iris transilluminatio n (see section 4.4)	
Ear and labyrinth disorders*			Tinnitus Hearing impairment incl. deafness (usually reversible)		
Cardiac disorders	QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmia s Syncope (i.e., acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de Pointes (see section 4.4) Cardiac arrest (see section 4.4)	
Vascular disorders		Vasodilatation	Hypertension Hypotension	Vasculitis	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)			
Gastro-intestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic-associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications, see section 4.4)		
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases, see section 4.4)	
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria Dry skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see section 4.4)	Acute Generalised Exanthematous Pustulosis (AGEP)
Musculo-skeletal and connective tissue disorders*		Arthralgia Myalgia	Tendonitis (see section 4.4) Muscle cramp Muscle twitching Muscle weakness	Tendon rupture (see section 4.4) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)	Rhabdo-myolysis

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Renal and urinary disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure (see section 4.4)		
General disorders and administration site conditions*	Injection and infusion site reactions	Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating Infusion site (thrombo-) phlebitis	Oedema		

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

The following undesirable effects have a higher frequency category in the subgroup of IV treated patients with or without subsequent oral therapy:

Common: Increased gamma-glutamyl-transferase

Uncommon: Ventricular tachyarrhythmias, hypotension, oedema, antibiotic-associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4), seizures incl. grand mal convulsions (see section 4.4), hallucination, renal impairment (incl. increase in BUN and creatinine), renal failure (see section 4.4)

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia, photosensitivity reactions (see section 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

No specific countermeasures after accidental overdose are recommended. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Concomitant administration of charcoal with a dose of 400 mg oral or intravenous moxifloxacin will reduce systemic availability of the drug by more than 80% or

20% respectively. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

PK/PD
Fluoroquinolones exhibit a concentration dependent killing of bacteria. Pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials indicate that the primary determinant of efficacy is the AUC_{24}/MIC ratio.

Mechanism of resistance
Resistance to fluoroquinolones can arise through mutations in DNA gyrase and topoisomerase IV. Other mechanisms may include over-expression of efflux pumps, impermeability, and protein-mediated protection of DNA gyrase. Cross resistance should be expected between moxifloxacin and other fluoroquinolones.
The activity of moxifloxacin is not affected by mechanisms of resistance that are specific to antibacterial agents of other classes.

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

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

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

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus**[+] *Streptococcus agalactiae* (Group B) *Streptococcus milleri* group* (*S. anginosus, S. constellatus and S. intermedius*) *Streptococcus pneumoniae** *Streptococcus pyogenes** (Group A) *Streptococcus viridans* group *(S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus)*
Aerobic Gram-negative micro-organisms *Acinetobacter baumanii* *Haemophilus influenzae** *Legionella pneumophila* *Moraxella (Branhamella) catarrhalis**
Anaerobic micro-organisms *Prevotella* spp.
"Other" micro-organisms *Chlamydophila (Chlamydia) pneumoniae** *Coxiella burnetii* *Mycoplasma pneumoniae**
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecalis** *Enterococcus faecium**
Aerobic Gram-negative micro-organisms *Enterobacter cloacae** *Escherichia coli**[#] *Klebsiella oxytoca* *Klebsiella pneumoniae**[#] *Proteus mirabilis**
Anaerobic micro-organisms *Bacteroides fragilis**
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Pseudomonas aeruginosa*
*Activity has been satisfactorily demonstrated in clinical studies. [+]Methicillin resistant *S. aureus* have a high probability of resistance to fluoroquinolones. Moxifloxacin resistance rate of > 50% have been reported for methicillin resistant *S. aureus*. [#]ESBL-producing strains are commonly also resistant to fluoroquinolones.

5.2 Pharmacokinetic properties

Absorption and Bioavailability

After a single 400 mg intravenous 1 hour infusion peak plasma concentrations of approximately 4.1 mg/l were observed at the end of the infusion corresponding to a mean increase of approximately 26% relative to those seen after oral administration (3.1 mg/l). The AUC value of approximately 39 mg·h/l after i.v. administration is only slightly higher than that observed after oral administration (35 mg·h/l) in accordance with the absolute bioavailability of approximately 91%.

In patients, there is no need for age or gender related dose adjustment on intravenous moxifloxacin.

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

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

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

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

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

Elimination
Moxifloxacin is eliminated from plasma with a mean terminal half-life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Following a 400 mg intravenous infusion recovery of unchanged drug from urine was approximately 22% and from faeces approximately 26%. Recovery of the dose (unchanged drug and metabolites) totalled to approximately 98% after intravenous administration of the drug. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

Renal impairment
The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance > 20 ml/min/1.73 m^2). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 m^2).

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

5.3 Preclinical safety data

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

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

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

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid 1 N (for pH-adjustment)
Sodium hydroxide solution 2 N (for pH-adjustment)
Water for injections

6.2 Incompatibilities

The following solutions are incompatible with moxifloxacin solution for infusion:
Sodium chloride 10% and 20% solutions
Sodium bicarbonate 4.2% and 8.4% solutions
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years
Use immediately after first opening and/or dilution.

6.4 Special precautions for storage

Store below 30°C but not below 15°C. Store in the original container.
Keep out of reach of children

6.5 Nature and contents of container

Colourless glass bottles (type 2) with a chlorobutyl or bromobutyl rubber stopper as closure. The 250 ml bottle is available in packs of 1 bottle.

6.6 Special precautions for disposal and other handling

This product is for single use only. Any unused solution should be discarded.
The following co-infusions were found to be compatible with moxifloxacin 400 mg solution for infusion:
Water for injections, Sodium chloride 0.9%, Sodium chloride 1 molar, Glucose 5%/10%/40%, Xylitol 20%, Ringer's solution, Compound Sodium Lactate Solution (Hartmann's Solution, Ringer-Lactate Solution).
Moxifloxacin solution for infusion should not be co-infused with other drugs.
Do not use if there are any visible particulate matter or if the solution is cloudy.
At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution below 15°C.

7. MANUFACTURER

Bayer AG
51368 Leverkusen
Germany

8. DATE OF REVISION OF THE TEXT

19/06/2020

PACKAGE LEAFLET

Package leaflet: Information for the user

Avelox 400 mg/250 ml solution for infusion
For use in adults.
Moxifloxacin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Avelox is and what it is used for

Avelox contains the active substance moxifloxacin which belongs to a group of antibiotics called fluoroquinolones. Avelox works by killing bacteria that cause infections if they are caused by bacteria that are susceptible to moxifloxacin.

Avelox is used in adults for treating the following bacterial infections:
- Infection of the lungs (pneumonia) acquired outside the hospital
- Infections of the skin and soft tissue

2. What you need to know before you are administered Avelox

Contact your doctor if you are not sure if you belong to a patient group described below.

Do not use Avelox
- If you are allergic to the active substance moxifloxacin, any other quinolone antibiotics or any of the other ingredients of this medicine (listed in section 6).
- If you are pregnant or breast-feeding.
- If you are under 18 years of age.
- If you have a history of tendon disease or disorder which was related to treatment with quinolone antibiotics (see sections *Warnings and precautions* and *4. Possible side effects*).
- If you were born with or have had any condition with abnormal heart rhythm (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called ‘bradycardia’), have a weak heart (heart failure), have a history of abnormal heart rhythms, or you are taking other medicines that result in abnormal ECG changes (see section *Other medicines and Avelox*). This is because Avelox can cause changes on the ECG, that is a prolongation of the QT-interval i.e. delayed conduction of electrical signals.
- If you have a severe liver disease or liver enzymes (transaminases) that are higher than 5 times the upper normal limit.

Warnings and precautions

Before taking this medicine
You should not take fluoroquinolone/quinolone antibacterial medicines, including Avelox, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

Talk to your doctor before Avelox is administered for the first time

- Avelox can **change your heart's ECG**, especially if you are female, or if you are elderly. If you are currently taking any **medicine that decreases your blood potassium levels**, consult your doctor before Avelox is administered (see also sections *Do not use Avelox* and *Other medicines and Avelox*).

- If you have ever developed **a severe skin rash or skin peeling, blistering and/or mouth sores** after taking moxifloxacin.

- If you suffer from **epilepsy** or a condition which makes you likely to have **convulsions**, tell your doctor before Avelox is administered.

- If you have or have ever had any **mental health problems**, consult your doctor before Avelox is administered.

- If you suffer from **myasthenia gravis** using Avelox may worsen the symptoms of your disease. If you think you are affected consult your doctor immediately.

- If you have been diagnosed with an **enlargement or "bulge" of a large blood vessel** (aortic aneurysm or large vessel peripheral aneurysm).

- If you have experienced a previous episode of **aortic dissection** (a tear in the aorta wall).

- If you have a family history of **aortic aneurysm or aortic dissection** or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet´s disease, high blood pressure, or known atherosclerosis).

- If you are **diabetic** because you may experience a risk of **change in blood sugar levels** with moxifloxacin.

- If you or any member of your family have **glucose-6-phosphate dehydrogenase deficiency** (a rare hereditary disease), inform your doctor, who will advise whether Avelox is suitable for you.

- Avelox should be given intravenously (in the vein) only, and should not be administered into an artery.

When using Avelox

- If you experience **palpitations or irregular heart beat** during the period of treatment, you should inform your doctor immediately. He/she may wish to perform an ECG to measure your heart rhythm.

- The **risk of heart problems** may increase with increase of the dose and the speed of the perfusion into your vein.

- There is a rare chance that you may experience a **severe, sudden allergic reaction** (an anaphylactic reaction/shock) even with the first dose, with symptoms that may include tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, treatment with Avelox solution for infusion has to be discontinued immediately.**

- Avelox may cause a **rapid and severe inflammation of the liver** which could lead to life-threatening liver failure (including fatal cases, see section *4. Possible side effects*). Please contact your doctor before you continue the treatment if you suddenly start to feel unwell or notice yellowing of the whites of the eyes, dark urine, itching of the skin, a tendency to bleed or disturbances of thought or wakefulness.

- **Serious skin reactions**
  Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalised exanthematous pustulosis (AGEP) have been reported with the use of moxifloxacin.
  - SJS/TEN can appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious skin rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications or be fatal.
  - AGEP appears at the initiation of treatment as a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The most common location: mainly localized on the skin folds, trunk, and upper extremities.

  If you develop a serious rash or another of these skin symptoms, stop taking moxifloxacin and contact your doctor or seek medical attention immediately.

- Quinolone antibiotics, including Avelox, may cause **convulsions**. If this happens, treatment with Avelox has to be discontinued.

- **Prolonged, disabling and potentially irreversible serious side effects.**
  Fluoroquinolone/quinolone antibacterial medicines, including Avelox, have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue, and severe sleep disorders.
  If you experience any of these side effects after taking Avelox, contact your doctor immediately prior to continuing treatment. You and your doctor will decide on continuing the treatment considering also an antibiotic from another class.

- You may rarely experience **symptoms of nerve damage (neuropathy)** such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking Avelox and inform your doctor immediately in order to prevent the development of potentially irreversible condition.

- You may experience **mental health problems** even when taking quinolone antibiotics, including Avelox, for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-injurious behaviour such as suicide attempts (see section *4. Possible side effects*). If you develop such reactions, treatment with Avelox has to be discontinued.

- You may develop **diarrhoea** whilst taking, or after taking, antibiotics including Avelox. If this becomes severe or persistent or you notice that your stool contains blood or mucus you should stop using Avelox immediately and consult your doctor. In this situation, you should not take medicines that stop or slow down bowel movement.

- **Pain and swelling in the joints and inflammation or rupture of tendons** may occur rarely (see sections *Do not use Avelox* and *4. Possible side effects*). Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur

within the first 48 hours of treatment and even up to several months after stopping of Avelox therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking Avelox, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- If you feel **sudden, severe pain in your abdomen, chest or back**, go immediately to an emergency room.

- If you are elderly with existing **kidney problems** take care that your fluid intake is sufficient because dehydration may increase the risk of kidney failure.

- If your **eyesight becomes impaired** or if your eyes seem to be otherwise affected, consult an eye specialist immediately (see sections *Driving and using machines* and *4. Possible side effects).*

- Fluoroquinolone antibiotics may cause an **increase of your blood sugar levels** above normal levels (hyperglycemia), or **lowering of your blood sugar levels** below normal levels (hypoglycaemia), potentially leading to loss of consciousness (hypoglycaemic coma) in severe cases (see section *4. Possible side effects*). If you suffer from diabetes, your blood sugar should be carefully monitored.

- Quinolone antibiotics may make your **skin** become more **sensitive to sunlight or UV light**. You should avoid prolonged exposure to sunlight or strong sunlight and should not use a sunbed or any other UV lamp while using Avelox.

- There is limited experience on use of sequential intravenous/oral Avelox for the treatment of infection of the lungs (pneumonia) acquired outside the hospital.

- The efficacy of Avelox in the treatment of severe burns, infections of deep tissue and diabetic foot infections with osteomyelitis (infections of the bone marrow) has not been established.

Children and adolescents
This medicine must not be administered to children and adolescents under the age of 18 because efficacy and safety have not been established for this age group (see section *Do not use Avelox*).

Other medicines and Avelox
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines besides Avelox.

For Avelox, be aware of the following:
- If you are using Avelox and other medicines that affect your heart there is an increased risk for altering your heart rhythm. Therefore, do not use Avelox together with the following medicines: Medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride), tricyclic antidepressants, some antimicrobials (e.g. saquinavir, sparfloxacin, intravenous erythromycin, pentamidine, antimalarials particularly halofantrine), some antihistamines (e.g. terfenadine, astemizole, mizolastine), and other medicines (e.g. cisapride, intravenous vincamine, bepridil and diphemanil).
- You must tell your doctor if you are taking other medicines that can lower your blood potassium levels (e.g. some diuretics, some laxatives and enemas [large doses] or corticosteroids [anti-inflammatory drugs], amphotericin B) or cause a slow heart rate because these can also increase the risk of serious heart rhythm disturbances while using Avelox.
- If you are currently taking oral anti-coagulants (e.g. warfarin), it may be necessary for your doctor to monitor your blood clotting times.

Avelox with food and drink
The effect of Avelox is not influenced by food including dairy products.

Pregnancy, breast-feeding and fertility
Do not use Avelox if you are pregnant or breast-feeding.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Animal studies do not indicate that your fertility will be impaired by using this medicine.

Driving and using machines
Avelox may make you feel dizzy or light-headed, you may experience a sudden, transient loss of vision, or you might faint for a short period. If you are affected in this way do not drive or operate machinery.

Avelox contains sodium
This medicine contains 787 milligrams (approximately 34 millimoles) sodium (main component of cooking/table salt) in each bottle with 250 milliliter solution for infusion. This is equivalent to 39.35% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Avelox

Avelox will always be given to you by a doctor or healthcare professional.

The recommended dose for adults is one bottle once daily.

Avelox is for intravenous use. Your doctor should ensure that the infusion is given at a constant flow over 60 minutes.

No adjustment of the dose is required in elderly patients, patients with a low bodyweight or in patients with kidney problems.

Your doctor will decide on the duration of your treatment with Avelox. In some cases your doctor may start your treatment with Avelox solution for infusion and then continue your treatment with Avelox tablets.
The duration of treatment depends upon the type of infection, and how well you respond to treatment but the recommended durations of use are:

- Infection of the lungs (pneumonia) acquired outside the hospital 7 - 14 days

Most patients with pneumonia were switched to oral treatment with Avelox tablets within 4 days.

- Infections of the skin and soft tissue 7 - 21 days

For patients with complicated skin and skin structure infections the mean duration of intravenous treatment was approximately 6 days and the average overall duration of treatment (infusion followed by tablets) was 13 days.

It is important that you complete the course of treatment, even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured, the infection may return or your condition may get worse, and you may also create a bacterial resistance to the antibiotic.

The recommended dose and duration of treatment should not be exceeded (see section *2. What you need to know before you are administered Avelox, Warnings and precautions*).

If you receive more Avelox than you should
If you are concerned that you may have been received too much Avelox, contact your doctor immediately.

If you miss a dose of Avelox
If you are concerned that you may have missed a dose of Avelox, contact your doctor immediately.

If you stop using Avelox
If the treatment with this medicine is stopped too soon your infection may not be completely cured. Consult your doctor if you wish to stop the treatment with Avelox solution for infusion or Avelox tablets before the end of the course of treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The **most serious side effects** observed during the treatment with Avelox are listed below:

If you notice
- an abnormal fast heart rhythm (rare side effect)
- that you suddenly start feeling unwell or notice yellowing of the whites of the eyes, dark urine, itching of the skin, a tendency to bleed or disturbances of thought or wakefulness (these can be signs and symptoms of fulminant inflammation of the liver potentially leading to life-threating liver failure (very rare side effect, fatal cases have been observed))
- serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms (very rare side effects, potentially life-threatening).
- a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis) (frequency of this side effect is “not known”)
- syndrome associated with impaired water excretion and low levels of sodium (SIADH) (very rare side effect)
- loss of consciousness due to severe decrease in blood sugar levels (hypoglycaemic coma) (very rare side effect)
- inflammation of blood vessels (signs could be red spots on your skin, usually on your lower legs or effects like joint pain) (very rare side effect)
- a severe, sudden generalised allergic reaction incl. very rarely a life-threatening shock (e.g. difficulty in breathing, drop of blood pressure, fast pulse) (rare side effect)
- swelling incl. swelling of the airway (rare side effect, potentially life-threatening)
- convulsions (rare side effect)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities (rare side effect)
- depression (in very rare cases leading to self-harm, such as suicidal ideations/thoughts, or suicide attempts) (rare side effect)
- insanity (potentially leading to self-harm, such as suicidal ideations/thoughts, or suicide attempts) (very rare side effect)
- severe diarrhoea containing blood and/or mucus (antibiotic associated colitis incl. pseudomembranous colitis), which in very rare circumstances, may develop into complications that are life-threatening (rare side effects)
- pain and swelling of the tendons (tendonitis) (rare side effect) or a tendon rupture (very rare side effect)

- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis) (frequency of this side effect is "not known").

stop taking Avelox and tell your doctor immediately as you may need urgent medical advice.

In addition, if you notice
- transient loss of vision (very rare side effect),
- discomfort or pain to the eyes, especially due to light exposure (very rare to rare side effect)

contact an eye specialist immediately.

If you have experienced life-threatening irregular heart beat (Torsade de Pointes) or stopping of heart beat while taking Avelox (very rare side effects), **tell your treating doctor immediately that you have taken Avelox and do not restart the treatment.**

A worsening of the symptoms of myasthenia gravis has been observed in very rare cases. If this happens, **consult your doctor immediately**.

If you suffer from diabetes and you notice that your blood sugar is increased or decreased (rare or very rare side effect), **inform your doctor immediately**.

If you are elderly with existing kidney problems and you notice decrease in urine output, swelling in your legs, ankles or feet, fatigue, nausea, drowsiness, shortness of breath or confusion (these can be signs and symptoms of kidney failure, a rare side effect), **consult your doctor immediately.**

Other side effects which have been observed during treatment with Avelox are listed below by how likely they are:

Common (may affect up to 1 in 10 people)
- nausea
- diarrhoea
- dizziness
- stomach and abdominal ache
- vomiting
- headache
- increase of a special liver enzyme in the blood (transaminases)
- infections caused by resistant bacteria or fungi e.g. oral and vaginal infections caused by Candida
- pain or inflammation at injection site
- change of the heart rhythm (ECG) in patients with low blood potassium level

Uncommon (may affect up to 1 in 100 people)
- rash
- stomach upset (indigestion/heartburn)
- changes in taste (in very rare cases loss of taste)
- sleep problems (predominantly sleeplessness)
- increase of a special liver enzyme in the blood (gamma-glutamyl-transferase and/or alkaline phosphatase)
- low number of special white blood cells (leukocytes, neutrophils)
- constipation
- itching
- sensation of dizziness (spinning or falling over)
- sleepiness
- wind
- change of the heart rhythm (ECG)

- impaired liver function (incl. increase of a special liver enzyme in the blood (LDH))
- decreased appetite and food intake
- low white blood cells count
- aches and pains such as back, chest, pelvic and extremities pains
- increase of special blood cells necessary for blood clotting
- sweating
- increased specialised white blood cells (eosinophils)
- anxiety
- feeling unwell (predominantly weakness or tiredness)
- shaking
- joint pain
- palpitations
- irregular and fast heart beat
- difficulty in breathing incl. asthmatic conditions
- increase of a special digestive enzyme in the blood (amylase)
- restlessness / agitation
- tingling sensation (pins and needles) and/or numbness
- skin hives
- widening of blood vessels
- confusion and disorientation
- decrease of special blood cells necessary for blood clotting
- visual disturbances incl. double and blurred vision
- decreased blood clotting
- increased blood lipids (fats)
- low red blood cell count
- muscle pain
- allergic reaction
- increase of bilirubin in the blood
- inflammation of a vein
- inflammation of the stomach
- dehydration
- severe heart rhythm abnormalities
- dry skin
- angina pectoris

Rare (may affect up to 1 in 1,000 people)
- muscle twitching
- muscle cramp
- hallucination
- high blood pressure
- swelling (of the hands, feet, ankles, lips, mouth, throat)
- low blood pressure
- kidney impairment (incl. increase in special kidney laboratory test results like urea and creatinine)
- inflammation of the liver
- inflammation of the mouth
- ringing/noise in the ears
- jaundice (yellowing of the whites of the eyes or skin)
- impairment of skin sensation
- abnormal dreams
- disturbed concentration
- difficulty in swallowing
- changes in smell (incl. loss of smell)
- balance disorder and poor co-ordination (due to dizziness)

- partial or total loss of memory
- hearing impairment including deafness (usually reversible)
- increased blood uric acid
- emotional instability
- impaired speech
- fainting
- muscle weakness

Very rare (may affect up to 1 in 10,000 people)
- a drop in the number of red and white blood cells and platelets (pancytopenia)
- inflammation of joints
- abnormal heart rhythms
- increase of skin sensitivity
- a feeling of self-detachment (not being yourself)
- increased blood clotting
- muscle rigidity
- significant decrease of special white blood cells (agranulocytosis)

Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), depression, fatigue, sleep disorders, memory impairment, as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

The following symptoms have been observed more frequently in patients treated intravenously:

Common (may affect up to 1 in 10 people)
- Increase of a special liver enzyme in the blood (gamma-glutamyl-transferase)

Uncommon (may affect up to 1 in 100 people)
- severe diarrhoea containing blood and/or mucus (antibiotic associated colitis) which in very rare circumstances, may develop into complications that are life-threatening
- abnormal fast heart rhythm
- hallucination
- low blood pressure
- kidney impairment (incl. increase in special kidney laboratory test results like urea and creatinine)
- kidney failure
- swelling (of the hands, feet, ankles, lips, mouth, throat)
- convulsions

Furthermore, there have been very rare cases of the following side effects reported following treatment with other quinolone antibiotics, which might possibly also occur during treatment with Avelox: raised pressure in the skull (symptoms include headache, visual problems including blurred vision, “blind” spots, double vision, loss of vision), increased blood sodium levels, increased blood calcium levels, a special type of reduced red blood cell count (haemolytic anaemia), increased sensitivity of the skin to sunlight or UV light.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Avelox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label of the bottle and on the carton. The expiry date refers to the last day of that month.

Store below 30°C but not below 15°C.

Use immediately after first opening and/or dilution.

This product is for single use only. Any unused solution should be discarded.
At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature.
Do not use this medicine if you notice any visible particulate matter or if the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Avelox contains

- The active substance is moxifloxacin. Each bottle contains 400 milligram moxifloxacin (as hydrochloride). 1 milliliter contains 1.6 milligram moxifloxacin (as hydrochloride).
- The other ingredients are sodium chloride, hydrochloric acid 1 N (for pH-adjustment), sodium hydroxide solution 2 N (for pH-adjustment) and water for injections (see section *Avelox contains sodium*).

What Avelox looks like and contents of the pack
Avelox is a clear, yellow solution for infusion.

Avelox is packaged in cartons containing a 250 milliliter glass bottle with a chlorobutyl or bromobutyl rubber stopper.

This leaflet was last revised in {June 2020}.