

AVELOX®

NAME OF THE MEDICINAL PRODUCT

Avelox 400 mg film-coated tablets

Avelox 400 mg/250mL solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablet

1 film-coated tablet contains 400 mg moxifloxacin (as hydrochloride).

Solution for infusion

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

PHARMACEUTICAL FORM

Film-coated tablet

Dull red film-coated tablet with an oblong, convex shape with facet, a dimension of 17x7 mm with 10 mm radius of curvature and a weight of 693.8-699.8mg. "Bayer" on one side and "M 400" on the other side.

Dull red film-coated tablet with an oblong, convex shape with facet, a dimension of 17x7 mm with 10 mm radius of curvature and a weight of 693.8-699.8mg. "blanc" on one side and "M 400" on the other side.

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.

INDICATIONS

Avelox tablets are indicated for the treatment of adults (≥ 18 years of age) with the following bacterial infections caused by susceptible strains:

- Acute sinusitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Mild to moderately severe inflammatory pelvic diseases (i.e. Infections of the upper female genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.

Avelox 400 mg film-coated tablets are not recommended for monotherapy of mild to moderately severe inflammatory pelvic diseases. Preferably, they should be

administered in combination with another suited antibiotic (such as cephalosporin), due to the increasing resistance of *Neisseria gonorrhoeae* to moxifloxacin; that is, unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be ruled out.

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections including polymicrobial infections such as abscesses

Avelox solution for infusion is indicated for the treatment of adults (≥ 18 years of age) with the following bacterial infections caused by susceptible strains:

- Community acquired pneumonia
- Complicated skin and skin structure infections
- Complicated intraabdominal infections including polymicrobial infections such as abscesses

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

Avelox should be only used:

- When *Pseudomonas fluorescens* is considered AND the patient is allergic to antipseudomonal penicillins/ cephalosporin; or
- For resistant organism with no other alternative antibiotics available (see section “*Pharmacodynamic properties*” for susceptibility data).

Avelox should not be used >24 hours post operation.

DOSAGE AND METHOD OF ADMINISTRATION

Dose (adults)

The recommended dose for Avelox is 400 mg once daily (1 film-coated tablet or 250 mL solution for infusion, respectively) for the above mentioned indications and should not be exceeded.

Duration of treatment

The duration of treatment should be determined by the severity of the indication or clinical response. The following general recommendations for the treatment of upper and lower respiratory tract infections are made:

Film-coated tablet:

Bronchitis: acute exacerbation of chronic bronchitis, 5 days

Pneumonia: community acquired pneumonia, 10 days

Sinusitis: acute sinusitis, 7 days

Mild to moderately severe inflammatory pelvic diseases: 14 days

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

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

Solution for infusion:

Therapy may be initial intravenous administration, followed by oral administration of film-coated tablets when clinically indicated.

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

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

Complicated intraabdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 5 – 14 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).

Method of administration Film-coated tablet:

The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

Solution for infusion:

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

A statement “Infuse over a period of 60 minutes” should be given on the primary packaging material of the infusion solution.

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 solution for infusion, 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 solution for infusion is to be given with another drug, each drug should be given separately (see “Pharmaceutical Particulars, Incompatibilities”). Only clear solutions are to be used.

Missed dose

If a dose is missed, it should be taken anytime but not later than 8 hours prior to the 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.

Geriatric patients

No adjustment of dosage is required in the elderly.

Pediatric patients

The efficacy of Avelox in children and adolescents has not been established. No recommendation on posology can be made.

The safety of Avelox in children below the age of 6 years has not been established.

Ethnic differences

No adjustment of dosage is required in ethnic groups.

Patients with hepatic impairment

No dosage adjustment is required in patients with impaired liver function (see also “*Special warnings and precautions for use*” in patients with liver cirrhosis).

Patients with renal impairment

No dose adjustment is required in patients with renal impairment (including creatinine clearance ≥ 30 mL/min/1.73m²) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis.

CONTRAINDICATIONS

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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 section “*Undesirable Effects*”). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Cases of acute myocardial ischemia with or without myocardial infarction as part of a hypersensitivity reaction (Kounis syndrome) have also been reported (see “*Undesirable Effects*”). In the event of Kounis syndrome while on treatment with moxifloxacin, discontinue Avelox immediately.

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 the infusion rate (400 mg within 60 minutes) should not be exceeded. However, in patients suffering from pneumonia no correlation between plasma concentrations of moxifloxacin and QTc prolongation was observed. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Avelox treatment in clinical studies with more than 9000 patients, however certain predisposing conditions may increase the risk for ventricular arrhythmias.

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

- 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

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

- 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 preexisting QT prolongation in these patients cannot be excluded.

- in women and elderly patients who, both, may be more susceptible to QTcprolonging drugs.

Hepatobiliary system

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with Avelox (see section “*Undesirable Effects*”). Patients should be advised to contact their doctor immediately prior to continuing treatment if symptoms related to liver failure occur.

Seizures

Seizures may occur with quinolone therapy. It should be used with caution in patients with known or suspected Central Nervous System (CNS) disorders which may predispose to seizures or lower the seizure threshold.

Gastrointestinal system

Antibiotic associated colitis has been reported with the use of broad-spectrum antibiotics including Avelox; therefore it is important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of Avelox. In this clinical situation adequate therapeutic measures should be initiated immediately. 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. Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

Prolonged, disabling and potentially irreversible serious adverse drug reactions Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. Avelox 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.

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 fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), 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 Avelox 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.

Complicated pelvic inflammatory disease For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with Avelox 400 mg filmcoated 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 polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Avelox 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 development of potentially irreversible condition (see “Undesirable effects”).

Psychiatric reactions

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

Genital tract infections

Because of the widespread and rising prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* infections, monotherapy with moxifloxacin should be avoided in patients with pelvic inflammatory disease, unless fluoroquinolone-resistant *N. gonorrhoeae* can be excluded. If fluoroquinolone-resistant *N. gonorrhoeae* can not 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.

Dysglycemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia 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. In diabetic patients, careful monitoring of blood glucose is recommended (see “Undesirable effects”)

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.

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.

Antacids, minerals and multi-vitamins

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

aluminum, 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.

Warfarin

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 Avelox 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.

PREGNANCY AND LACTATION

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.

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.

Effects on ability to drive or use machines

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see section “*Undesirable Effects*”).

UNDESIRABLE EFFECTS

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 from sequential/intravenous therapy studies; status: May 2010) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and 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 ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$),
 very rare ($< 1/10,000$)

Not known: frequency cannot be estimated from the available data

System Organ Class (MEDRA)	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Mycotic superinfections				
Blood and the lymphatic system disorders		Anemia Leukopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Prothrombin time prolonged / INR increased	Thromboplastin level abnormal	Prothrombin level increased / INR decreased Prothrombin level / INR abnormal	

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 lability Depression (<i>in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideation / thoughts or suicide attempts</i>) Hallucinations	Depersonalization Psychotic reactions, (<i>potentially culminating in self-injurious behaviour, such as suicidal ideation / thoughts or suicide attempts</i>)	
Nervous system	Headache	Par- and	Hypoesthesia	Hyperesthesia	

disorders#	Dizziness	Dysesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders Tremor Vertigo Somnolence	Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; <i>in very rare cases leading to fall with injuries, esp. in elderly</i>) Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy		
Eye disorders#		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)	
Ear and labyrinth disorders#			Tinnitus Hearing impairment including deafness (usually reversible)		
Cardiovascular system disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes * Cardiac arrest *	Kounis syndrome #

				<i>* (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia , acute myocardial ischemia)</i>	
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-glutamyltransferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	<i>Fulminant hepatitis potentially leading to lifethreatening liver failure(incl. fatal cases)</i>	

Skin and subcutaneous tissue disorders				<i>Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)</i>	
Musculoskeletal, connective tissue and bone disorders#		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	<i>Tendon rupture</i> Arthritis	
Renal and urinary disorders		<i>Dehydration (caused by diarrhea or reduced fluid intake)</i>	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		

Acute myocardial ischaemia with or without myocardial infarction as part of a hypersensitivity reaction (see Special warnings and precautions for use)
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 disturbances 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), Hallucinations, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)

Post Marketing Experience

Exacerbation of symptoms of myasthenia gravis.

Additional information on special populations

Pediatric patients

Adverse reactions in children (>3 months - <18 years) were derived from a clinical study in pediatric patients with complicated intra-abdominal infection. For the safety analysis, data from a total of 301 pediatric patients treated with moxifloxacin were available, thereof 15 patients below the age of 6 years and 286 patients at the age of 6 - <18 years.

Cartilage damage of weight-bearing joints in juvenile animals is a known class effect of fluoroquinolones. Therefore, musculoskeletal events were carefully monitored and followed up over 1 year after the study treatment. The musculoskeletal adverse events observed in the study were mostly rated as mild in intensity, and were equally distributed among the moxifloxacin and the comparator groups. There were no events indicating chondropathy.

Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients (see Special warnings and precautions for use). The ECG analyses in pediatric patients revealed that QT prolongation is common. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in the pediatric study. For specific warnings and precautions for use referring to QT prolongation, see Special warnings and precautions for use.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. Sub-set analyses by age groups did not reveal any age-related exceptions. However, the low number of children below the age of 6 years limits the analysis of adverse reactions in younger children.

OVERDOSE

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

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

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones

ATC Code: J01MA 14

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 e.g. *Chlamydia* spp., *Mycoplasma* spp. and *Legionella* spp.

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

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

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

Resistance

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

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

In vitro studies have demonstrated that resistance to moxifloxacin develops slowly by multiple step mutations. A very low overall frequency of resistance was demonstrated

(10^{-7} – 10^{-10}). Serial exposure of organisms to sub-MIC concentrations of moxifloxacin showed only a small increase in MIC values.

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

Effect on the intestinal flora in humans

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

In vitro Susceptibility Data

Susceptible	Intermediate	Resistant
Gram-positive bacteria		
<i>Gardnerella vaginalis</i>		
<i>Streptococcus pneumoniae</i> * including multi-drug resistant streptococcus pneumoniae strains [MDRSP] including strains known as PRSP (Penicillin-resistant <i>S. pneumoniae</i>), and strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 μ g/mL), 2 nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole		
<i>Streptococcus pyogenes</i> (group A)*		
<i>Streptococcus milleri</i> group (<i>S. anginosus</i> *, <i>S. constellatus</i> *, and <i>S. intermedius</i> *)		
<i>Streptococcus viridans</i> group (<i>S. viridans</i> , <i>S. mutans</i> , <i>S. mitis</i> , <i>S. sanguinis</i> , <i>S. salivarius</i> , <i>S. thermophilus</i> , <i>S. constellatus</i>)		
<i>Streptococcus agalactiae</i>		

<i>Streptococcus dysgalactiae</i>		
<i>Staphylococcus aureus</i> (methicillin susceptible strains) *		<i>Staphylococcus aureus</i> (methicillin/ofloxacin resistant strains) ⁺
Coagulase negative Staphylococci (<i>S. cohnii</i> , <i>S. epidermidis</i> , <i>S. haemolyticus</i> , <i>S. hominis</i> , <i>S. saprophyticus</i> , <i>S. simulans</i>) methicillin susceptible strains.		Coagulase negative Staphylococci (<i>S. cohnii</i> , <i>S. epidermidis</i> , <i>S. haemolyticus</i> , <i>S. hominis</i> , <i>S. saprophyticus</i> , <i>S. simulans</i>) methicillin resistant strains
	<i>Enterococcus faecalis</i> * (Vancomycin, Gentamycin, susceptible strains only)	
	<i>Enterococcus avium</i> *	
	<i>Enterococcus faecium</i> *	

*/** 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		
<i>Haemophilus influenzae</i> (including β lactamase negative and positive strains) *		
<i>Haemophilus parainfluenzae</i> *		
<i>Moraxella catarrhalis</i> (including β lactamase negative and positive strains) *		
<i>Bordetella pertussis</i>		
<i>Legionella pneumophila</i>	<i>Escherichia coli</i> *	
<i>Acinetobacter baumannii</i>	<i>Klebsiella pneumoniae</i> *	
	<i>Klebsiella oxytoca</i>	
	<i>Citrobacter freundii</i> *	

	<i>Enterobacter</i> species (<i>E. aerogenes</i> , <i>E. intermedius</i> , <i>E. sakazaki</i>)	
	<i>Enterobacter cloacae</i> *	
	<i>Pantoea agglomerans</i>	
		<i>Pseudomonas aeruginosa</i>
	<i>Pseudomonas fluorescens</i>	
	<i>Burkholderia cepacia</i>	
	<i>Stenotrophomonas maltophilia</i>	
	<i>Proteus mirabilis</i> *	
<i>Proteus vulgaris</i>		
	<i>Morganella morganii</i>	
	<i>Neisseria gonorrhoea</i> **	
	<i>Providencia</i> species (<i>P. rettgeri</i> , <i>P. stuartii</i>)	
<i>Yersinia pestis</i>		

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

Susceptible	Intermediate	Resistant
Anaerobes		
	<i>Bacteroides</i> sp (<i>B. fragilis</i> *, <i>B. distasoni</i> *, <i>B. thetaiotaomicron</i> *, <i>B. ovatus</i> *, <i>B. uniformis</i> *, <i>B. vulgaris</i> *)	
<i>Fusobacterium</i> spp		
	<i>Peptostreptococcus</i> spp. *	
<i>Porphyromonas</i> spp		
<i>Prevotella</i> spp		
<i>Propionibacterium</i> spp.	<i>Clostridium</i> sp *	

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

Susceptible	Intermediate	Resistant
Atypicals		
<i>Chlamydia pneumoniae</i> *		
<i>Chlamydia trachomatis</i> **		
<i>Mycoplasma pneumoniae</i> *		

<i>Mycoplasma hominis</i>		
<i>Mycoplasma genitalum</i>		
<i>Coxiella burnettii</i>		

*/** 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/MIC₉₀ parameters greater than 125 and C_{max} / MIC₉₀ of 8 – 10 is predictive for clinical cure (Schentag). In outpatients these surrogate parameters are generally smaller, i.e. AUC/MIC₉₀ greater than 30-40 (Dudley and Ambrose).

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

Mode of administration	Intravenous		oral	
Parameter (median)	AUC [h]	C _{max} /MIC ₉₀ a)	AUC [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

PHARMACOKINETIC PROPERTIES

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 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.

Distribution

Moxifloxacin is distributed very rapidly to extra vascular spaces. Exposure to drug in terms of AUC ($AUC_{norm} = 6 \text{ kg} \cdot \text{h/L}$) 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 > 10x 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.

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

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	1.61 mg/L	1.71
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	1.751	mg/L	1.71
Interstitial fluid	1.0 ²	mg/L	0.8 – 2.5 ^{2,3}
Abdominal tissue ⁴	7.03	mg/kg	1.56
Abdominal exsudate ⁵	3.32	mg/L	1.45
Female genital tract ⁴	10.2	mg/kg	1.72
Abscess fluid ⁶	1.94	mg/L	0.74

- 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.

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.

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 approx. 96-98% independent from the route of administration with no indication of oxidative metabolism. A detailed overview of mass balance according to elimination pathways (renal vs non-renal, metabolic vs. nonmetabolic) and mode of application is given in the table below.

Recovery of a 400 mg single dose (arithmetic mean $\pm$ standard deviation (SD))

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

Geriatric patients

Pharmacokinetics of moxifloxacin are not affected by age.

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.

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.

Pediatric patients

Pharmacokinetics of moxifloxacin were studied after single dose intravenous (i.v.) administration (1h infusion) in pediatric patients ranging from 3 months to < 14 years. The corresponding PK parameters are summarized in the subsequent table.

Geometric mean/ CV (%) for PK Parameters of Moxifloxacin in Pediatric Patients After Single Intravenous Administration of Moxifloxacin as 1h Infusion

Age group	3 months to < 2 years		2 to <6 years		6 to <14 years	
Dose	9 mg/kg (n=6)	10 mg/kg (n=1)	7 mg/kg (n=7)	8 mg/kg (n=5)	5 mg/kg (n=7)	6 mg/kg (n=5)
Variable AUC (mg*h/L)	25.52/17.26	40.5/-	28.21/2.75	27.18/19.29	19.73/30.53	24.04/4.11
Cmax (mg/L)	5.31/4.67	5.96/-	6.51/43.54	5.64/10.71	3.16/33.33	4.61/17.10
t1/2 (h)	6.82/35.1	5.94/-	5.66/18.79	6.03/24.78	7.89/34.32	6.16/23.99
AeUr(%)	-	-	31.3/32.38	24.7/54.41	22.9/33.23	25.4/27.50

AeUr = amount excreted into urine; AUC = area under the curve; Cmax = maximum drug concentration in plasma after single dose administration; CV = coefficient of variation; t1/2 = half life

These data were used to derive oral and i.v. dosing schemes for a clinical Phase III study in pediatric patients as outlined in section Pharmacodynamic properties. A population PK analysis of data from Phase III with i.v. and sequential i.v. to oral treatment confirmed that the dosing schemes lead to a systemic moxifloxacin exposure which is comparable to the exposure seen in adult subjects. This is in the effective range for antimicrobial treatment based on PK/PD considerations (AUC/MIC). For pediatric patients <12 years of age and <45 kg body weight a switch from once daily to bid dosing is suitable to avoid overly high peak concentrations. The absolute bioavailability of moxifloxacin was estimated at 86%.

Patients with renal impairment

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

Patients with hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see “Special Warnings and Precautions for use” in patients with liver cirrhosis).

Preclinical safety data

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

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

Carcinogenicity, Mutagenicity

Although conventional long-term studies to determine the carcinogenic potential of moxifloxacin have not been performed, the drug has been subject to a range of *in vitro* and *in vivo* genotoxicity tests. In addition, an accelerated bioassay for human carcinogenesis (initiation/promotion assay) was performed in rats. Negative results were obtained in 4 strains of the Ames test, in the HPRT mutation assay in Chinese hamster ovary cells and in the UDS assay in rat primary hepatocytes. As with other fluoroquinolones the Ames test with TA 102 was positive and the *in vitro* test in the Chinese hamster v79 cells showed chromosomal abnormalities at high concentrations (300 mcg/mL). However, the *in vivo* micronucleus assay in the mouse was negative. An additional *in vivo* assay, the dominant lethal assay in the mouse, was negative as well. It is concluded that the negative *in vivo* results adequately reflect the *in vivo* situation in terms of genotoxicity. No evidence of carcinogenicity was found in an initiation/promotion assay in rats.

Phototoxicity

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

ECG

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

therapeutic level after intravenous administration), reversible, non-fatal ventricular arrhythmias were seen.

Oculotoxicity

Toxicity tests in rats and monkeys (repeated dosing up to six months) revealed no indication regarding an oculotoxic risk. In dogs, high oral doses (≥ 60 mg/kg) leading to plasma concentrations ≥ 20 mg/L caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

Arthrotoxicity

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

Reprotoxicity

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (per os and i.v.) and monkeys (per os) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. Skeletal malformations were observed in rabbits that had been treated with an intravenous dose of 20 mg/kg. This study result is consistent with the known effects of fluoroquinolones on skeletal development (see section “*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.

PHARMACEUTICAL PARTICULARS

List of excipients Film-coated

tablets:

Excipients:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Film-coating: ferric oxide red, hypromellose 15cP, macrogol 4000, titanium dioxide.

Solution for infusion:

hydrochloric acid 1N, sodium chloride sodium hydroxide solution 2N, water for injection.

Incompatibilities Film-coated tablets:

Not applicable.

Solution for infusion:

The following coinfusions were found to be incompatible with Avelox solution for infusion:

Sodium Chloride 10%

Sodium Chloride 20%

Sodium Hydrogen Carbonate 4.2%

Sodium Hydrogen Carbonate 8.4%

Shelf life

Please refer to label.

Special precautions for storage Film-coated tablet:

Do not store above 30°C. Store in the original package in order to protect from moisture

Solution for infusion:

Do not store above 30°C.

Do not refrigerate or freeze.

Store in the original container.

Nature and contents of container

Film-coated tablet: Blister comprising polypropylene foil sealed with aluminium backing foil, in a cardboard outer.

Solution for infusion: Polyolefine flexibags equipped with an administration port and overwrapped with an aluminium bag or Infusion bottles of colourless glass (type 2) sealed with PTFE-laminated chlorobutyl rubber stoppers.

Instructions for use / handling Film-coated tablet:

None

Solution for infusion:

At temperatures below 15°C precipitation may occur, which will re-dissolve at room temperature (15°C - 25°C). 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 from particles should be used.

Presentation

Avelox 400 mg film-coated tablets – Blister pack of 5's

Avelox 400 mg/ 250ml solution for infusion – 5 glass vial/pack or 1 infusion solution flexibag

Not all pack sizes and presentations are marketed.

Manufacturer

Film-coated tablet:

Bayer HealthCare Manufacturing S.r.l.

Via delle Groane 126

20024 Garbagnate Milanese

Italy

Solution for infusion:

Fresenius Kabi Italia S.r.l

Via Camagre, 41/43

37063 Isola della Scala (VR)

Italy

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