1. NAME OF THE MEDICINAL PRODUCT

Avelox 400 mg film-coated tablets

Avelox 400 mg solution for infusion

2. 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).

For the full list of excipient(s) see section 'List of excipients'.

3. PHARMACEUTICAL FORM

Film-coated tablet

Dull red film-coated tablet with an oblong, convex shape with facet, a dimension of 17 x 7 mm with 10 mm radius of curvature and a weight of 693.8-699.8 mg. "Bayer" 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 filed with minimum 250 mL.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Avelox 400 mg film-coated tablets are indicated for the treatment of the following bacterial infections caused by susceptible strains:

- Respiratory tract infections:
  - Acute exacerbations of chronic bronchitis
  - Community acquired pneumonia (CAP) including CAP caused by multi-drug resistant strains*
  - Acute sinusitis
- Uncomplicated skin and skin structure infections
- Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis)
- Complicated skin and skin structure infections (incl. diabetic foot infections)
- Complicated intraabdominal infections including polymicrobial infections such as abscesses

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

- Community acquired pneumonia (CAP) including CAP caused by multi-drug resistant strains*
- Complicated skin and skin structure infections (incl. diabetic foot infections)
- Complicated intraabdominal infections including polymicrobial infections such as abscesses

*) Multi-drug resistant *Streptococcus pneumoniae* (MDRSP) includes isolates known as PRSP (Penicillin-resistant *S. pneumoniae*), and strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

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

4.2 Dosage and method of administration

4.2.1 Method of administration

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.

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

The following co-infusions 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.

4.2.2 Dosage regimen

Dose (adults)

The recommended dose for Avelox is 400 mg once daily (1 film-coated tablet and 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 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
Uncomplicated skin and skin structure infections:		7 days
Uncomplicated pelvic inflammatory disease:		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).

4.2.3 Missed dose

If a dose is missed, it should be taken as soon as the patient remembers on the same day. Double doses should not be taken to compensate for a missed dose.

4.2.4 Additional information on special populations

4.2.4.1 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.

4.2.4.2 Geriatric patients

No adjustment of dosage is required in elderly.

4.2.4.3 Patients with hepatic impairment

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

4.2.4.4 Patients with renal impairment

No dose adjustment is required in patients with renal impairment (including creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis.

4.2.4.5 Ethnic differences

No adjustment of dosage is required in ethnic groups.

4.3 Contraindications

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

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Hypersensitivity

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

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

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Avelox (see *"Undesirable Effects"*). Patients should be advised to

contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Cardiac disorder

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 moxifloxacin 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 QTc-prolonging drugs

Hepatobiliary system

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

Seizures

Seizures may occur with fluoroquinolone therapy. It should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history

of convulsion, reduced cerebral blood flow, altered brain structure or stroke), which may predispose to seizures or lower the seizure threshold.

Gastrointestinal system

Antibiotic associated colitis has been reported with the use of broad-spectrum antibiotics including 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 diarrhea.

Myasthenia gravis

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

Tendinitis and tendon rupture

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

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 film-coated tablets is not recommended.

MRSA infections

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

Interaction with tests

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

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paresthesias, hypoesthesias, dysesthesias, or weakness have been reported in patients receiving quinolones including Avelox. 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 (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 hypoglycemia and hyperglycemia have been reported with Avelox. In Avelox-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 moxifloxacin increased C_{max} of digoxin by approximately 30 % at steady state without affecting AUC or trough levels.

Charcoal

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

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

Food and dairy products

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

4.6 Pregnancy and lactation

4.6.1 Pregnancy

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

Consequently, the use of Avelox during pregnancy is contraindicated.

4.6.2 Lactation

As with other fluoroquinolones, Avelox has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There is no data available in lactating or nursing women. Therefore, the use of Avelox in nursing mothers is contraindicated.

4.7 Effects on ability to drive 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 "*Undesirable Effects*").

4.8 Undesirable effects

4.8.1 Tabulated list of adverse reactions

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

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare
Infections and infestations	Mycotic super-infections			
Blood and the lymphatic system disorders		Anemia Leukopenia(s) Neutropenia Thrombo-cytopenia Thrombo-cythemia Prothrombin time prolonged / INR increased	Thromboplastin level abnormal	Prothrombin level increased / INR decreased Prothrombin level / INR abnormal
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)

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression ***(in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts)*** Hallucinations	Depersonalization Psychotic reactions, ***(potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts)***
Nervous system disorders	Headache Dizziness	Par- and Dysesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders Tremor Vertigo Somnolence	Hypoesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; ***in very rare cases leading to fall with injuries, esp. in elderly***) Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and	Hyperesthesia

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare
			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 tachy-arrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias ***Torsade de Pointes **** ***Cardiac arrest **** **** (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)***
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepato-biliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	***Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)***
Skin and subcutaneous tissue disorders				***Bullous skin reactions like Stevens-Johnson-Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)***

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very rare
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	***Tendon rupture*** Arthritis ***Gait disturbance (caused by muscular, tendon or joint symptoms)*** ***Exacerbation of symptoms of myasthenia gravis***
Renal and urinary disorders		***Dehydration (caused by diarrhea or reduced fluid intake)***	Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General disorders and administration site conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Edema	

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

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

Common: Increased gamma-glutamyl-transferase

Uncommon: Ventricular tachyarrhythmias, Hypotension, Edema, Antibiotic associated colitis (in very rare cases associated with life threatening complications), Seizures of various clinical manifestations (incl. grand mal convulsions), Hallucinations, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)

4.8.2 Additional information on special populations

4.8.2.1 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.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones

ATC Code: J01MA14

5.1.1 Mechanism of action

Moxifloxacin is a 8-methoxy-fluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. Moxifloxacin has *in vitro* activity against a wide range of gram-positive

and gram-negative organisms, anaerobes, acid-fast bacteria, and atypicals 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.

5.2 Pharmacokinetic properties

5.2.1 Absorption and bioavailability

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

Pharmacokinetics are linear in the range of 50 - 1200 mg single dose and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/L are reached within 0.5 - 4 h 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 h 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 (1h 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 1h infusion.

5.2.2 Distribution

Moxifloxacin is distributed very rapidly to extra vascular spaces. Exposure to drug in terms of AUC (AUC_{norm} = 6 kg*h/L) is high with a volume of distribution at steady state (V_{ss}) of approx. 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.

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

5.2.3 Metabolism

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

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

5.2.4 Elimination

Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 mL/min. Renal clearance amounted to about 24 - 53 mL/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of ranitidine and probenecid did not alter renal clearance of the drug.

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.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets:

Excipients:

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

Film-Coating:

ferric oxide red,
hypromellose 15 cP,
macrogol 4000,
titanium dioxide.

Solution for infusion:

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

6.2 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%

6.3 Shelf life

Film-coated tablet:

5 years. Do not store above 25°C.

Solution for infusion:

Flexible bag: 3 years. Do not store below 15°C.

Glass bottle: 5 years. Do not store below 15°C.

6.4 Special precautions for storage

Film-coated tablet: None

Solution for infusion: Do not store below 15°C.

Store in the original container.

6.5 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.

CCDS 22, 10 May 2019

For further information please contact

Bayer Thai Co., Ltd., Bangkok