Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Avelox 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg moxifloxacin as hydrochloride.
Excipient: The film-coated tablet contains lactose monohydrate (see section 4.4).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from Greece:
Dull red tablets marked with “M400” on one side and “BAYER” on the reverse

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Avelox 400 mg film-coated tablets are indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin (see sections 4.4, 4.8 and 5.1). 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 or when these have failed:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia, except severe cases
- Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.
  Avelox 400 mg film-coated tablets are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of *Neisseria gonorrhoeae* unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded (see sections 4.4 and 5.1).

Avelox 400 mg film-coated tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:
- Community-acquired pneumonia
- Complicated skin and skin structure infections
Avelox 400 mg film-coated tablets should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia.

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

4.2 Posology and method of administration

Dosage (adults)
One 400 mg film-coated tablet once daily.

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.

Children and adolescents
Moxifloxacin is contraindicated in children and adolescents (< 18 years). Efficacy and safety of moxifloxacin in children and adolescents have not been established (see section 4.3).

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

Duration of administration
Avelox 400 mg film-coated tablets should be used for the following treatment durations:
- Acute exacerbation of chronic bronchitis 5 - 10 days
- Community acquired pneumonia 10 days
- Acute bacterial sinusitis 7 days
- Mild to moderate pelvic inflammatory disease 14 days

Avelox 400 mg film-coated tablets have been studied in clinical trials for up to 14 days treatment.

The recommended dose (400 mg once daily) and duration of therapy for the indication being treated should not be exceeded.

4.3 Contraindications

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.
- 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

- 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 these cases moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

- Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was 6 msec ± 26 msec, 1.4% compared to baseline. 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.
  Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin.
  Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest (see also section 4.3). The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.
  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.
  If signs of cardiac arrhythmia occur during treatment with moxifloxacin, treatment should be stopped and an ECG should be performed.
- 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.
- Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.
- Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders which may predispose to seizures or lower the seizure threshold.
- Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones. 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 (see section 4.8).
- 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.
- Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.
- Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin and rest the affected limb(s).
- 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.
- 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).
- 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 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.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

- 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.
- Pelvic inflammatory disease may be caused by fluoroquinolone resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.
- 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).
- 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).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products
An additive effect on QT interval prolongation between moxifloxacin and the following drugs cannot be excluded: antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide) or antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride), tricyclic antidepressive agents, certain antimicrobials (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine), certain antihistaminics (terfenadine, astemizole, mizolastine), others (cisapride, vincamine IV, bepridil, diphemanil). This effect might lead to an increased risk of ventricular arrhythmias, notably torsade de pointes. Therefore moxifloxacin is contraindicated in patients treated with these drugs (see also section 4.3).

An interval of about 6 hours should be left between administration of agents containing bivalent or trivalent cations (e.g. antacids containing magnesium or aluminium, didanosine tablets, sucralfate and agents containing iron or zinc) and administration of moxifloxacin.

Concomitant administration of charcoal with an oral dose of 400 mg moxifloxacin leads to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended (except for overdose cases, see also section 4.9).

After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin 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 antibiotics, 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 antibiotic therapy cause 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. Even if during an interaction study performed in healthy volunteers between moxifloxacin and warfarin, negative results have been observed, the precautionary measures as above stated should apply to warfarin as for other anticoagulants.

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

In vitro studies with human cytochrome P450 enzymes support this data. 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 use of moxifloxacin during pregnancy is contraindicated. The safety of moxifloxacin in human pregnancy has not been evaluated. Reversible joint injuries are described in children receiving some quinolones, however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lactation
The use of moxifloxacin during breast feeding is contraindicated. As with other quinolones, moxifloxacin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical data indicate that moxifloxacin passes into milk.

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 based on all clinical trials with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below:

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

System Organ Class	**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
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 Agranulocytosis
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)	
Metabolism and Nutrition Disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression (in very rare cases potentially culminating in self-endangering behaviour, such as suicidal ideations/ thoughts, or suicide attempts) Hallucination	Depersonalization Psychotic reactions (potentially culminating in self-endangering behaviour, such as suicidal ideations/ thoughts, or suicide attempts)
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	Hyperaesthesia
Eye Disorders		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)		Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment incl. deafness (usually reversible)	
Cardiac and Vascular Disorders	QT prolongation in patients with hypokalaemia (see section 4.4)	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris Vasodilatation	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness) Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes (see section 4.4) Cardiac arrest (see section 4.4)

Respiratory, Thoracic and Mediastinal Disorders		Dyspnea (including asthmatic conditions)		
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Anorexia Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (incl. pseudomembranous 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)
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis (see section 4.4) Muscle cramp Muscle twitching	Tendon rupture (see section 4.4) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)
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		Feeling unwell (predominantly asthenia or fatigue) Painful conditions	Oedema	

		(incl. pain in back, chest, pelvic and extremities) Sweating		

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: hypernatraemia, hypercalcaemia, haemolytic anaemia, rhabdomyolysis, photosensitivity reactions, peripheral neuropathy (see section 4.4).

4.9 Overdose

No specific countermeasures after accidental overdose are recommended. General symptomatic therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg oral moxifloxacin will reduce systemic availability of the drug by more than 80%. 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: J01 MA 14

Mechanism of action
Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative pathogens.
The bactericidal action of moxifloxacin results from the inhibition of both type II topoisomerases (DNA gyrase and topoisomerase IV) required for bacterial DNA replication, transcription and repair. 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, associated with the *nor*A or *pmr*A genes seen in certain Gram-positive bacteria.
Pharmacodynamic investigations have demonstrated that moxifloxacin exhibits a concentration dependent killing rate. Minimum bactericidal concentrations (MBC) were found to be in the range of the minimum inhibitory concentrations (MIC).

Interference with culture test
Moxifloxacin therapy may give false negative culture results for *Mycobacterium* spp. by suppression of mycobacterial growth.

Effect on the intestinal flora in humans
The following changes in the intestinal flora were seen in volunteers following oral administration of moxifloxacin: *Escherichia coli*, *Bacillus* spp., *Enterococcus* spp., and *Klebsiella* spp. were reduced, as were the anaerobes *Bacteroides vulgatus*, *Bifidobacterium* spp., *Eubacterium* spp., and *Peptostreptococcus* spp.. For *Bacteroides fragilis* there was an increase. These changes returned to normal within two weeks.

Mechanism of resistance
Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also effect susceptibility to moxifloxacin.
In vitro resistance to moxifloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Moxifloxacin is a poor substrate for active efflux mechanisms in Gram-positive organisms.
Cross-resistance is observed with other fluoroquinolones. However, as moxifloxacin inhibits both topoisomerase II and IV with similar activity in some Gram-positive bacteria, such bacteria may be resistant to other quinolones, but susceptible to moxifloxacin.

In vitro Susceptibility Data

EUCAST clinical MIC breakpoints for moxifloxacin (31.01.2006):

Organism	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 0.5 mg/l	> 1 mg/l
S. pneumoniae	≤ 0.5 mg/l	> 0.5 mg/l
Streptococcus Groups A, B, C, G	≤ 0.5 mg/l	> 1 mg/l
H. influenzae and *M. catarrhalis*	≤ 0.5 mg/l	> 0.5 mg/l
Enterobacteriaceae	≤ 0.5 mg/l	> 1 mg/l
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 (Gram-negative anaerobes).		

Clinical and Laboratory Standards Institute™ (CLSI), formerly NCCLS breakpoints are presented in the below table for MIC testing (mg/l) or disc diffusion testing (zone diameter [mm]) using a 5-µg moxifloxacin disc.

Clinical and Laboratory Standards Institute™ (CLSI) MIC and disc diffusion breakpoints for *Staphylococcus* spp. and fastidious organisms (M100-S17, 2007) and MIC breakpoints for anaerobes (M11-A7, 2007):

Organism	**Susceptible**	**Intermediate**	**Resistant**
S. pneumoniae	≤ 1 mg/l ≥ 18 mm	2 mg/l 15 - 17 mm	≥ 4 mg/l ≤ 14 mm
Haemophilus spp.	≤ 1 mg/l ≥ 18 mm	- -	- -
Staphylococcus spp.	≤ 0.5 mg/l ≥ 24 mm	1 mg/l 21 - 23 mm	≥ 2 mg/l ≤ 20 mm
Anaerobes	≤ 2 mg/l	4 mg/l	≥ 8 mg/l

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 *Gardnerella vaginalis* *Staphylococcus aureus** (methicillin-susceptible) *Streptococcus agalactiae* (Group B) *Streptococcus milleri* group* (*S. anginosus, S. constellatus and S. intermedius*) *Streptococcus pneumoniae** *Streptococcus pyogenes** (Group A)
Aerobic Gram-negative micro-organisms *Haemophilus influenzae** *Haemophilus parainfluenzae** *Klebsiella pneumoniae**[#] *Moraxella (Branhamella) catarrhalis**
Anaerobic micro-organisms *Fusobacterium* spp. *Peptostreptococcus* spp.

Prevotella spp.
"Other" micro-organisms *Chlamydophila (Chlamydia) pneumoniae** *Chlamydia trachomatis** *Coxiella burnetii* *Legionella pneumophila* *Mycoplasma genitalium* *Mycoplasma hominis* *Mycoplasma pneumoniae**
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Staphylococcus aureus* (methicillin-resistant)$^{+}$
Aerobic Gram-negative micro-organisms *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca* *Neisseria gonorrhoeae**$^{+}$
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Pseudomonas aeruginosa*
*Activity has been satisfactorily demonstrated in susceptible strains in clinical studies in the approved clinical indications. $^{\#}$ESBL-producing strains are commonly resistant to fluoroquinolones $^{+}$Resistance rate > 50% in one or more countries

5.2 Pharmacokinetic properties

Absorption and Bioavailability

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

Pharmacokinetics are linear in the range of 50 - 800 mg single dose and up to 600 mg once daily dosing over 10 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 h post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively. At steady-state the exposure within the dosing interval is approximately 30% higher than after the first dose.

Distribution

Moxifloxacin is distributed to extravascular spaces rapidly; after a dose of 400 mg an AUC of 35 mg·h/l is observed. 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.

The following peak concentrations (geometric mean) were observed following administration of a single oral dose of 400 mg moxifloxacin:

Tissue	Concentration	Site: Plasma ratio
Plasma	3.1 mg/l	-
Saliva	3.6 mg/l	0.75 - 1.3
Blister fluid	1.6[1] mg/l	1.7[1]
Bronchial mucosa	5.4 mg/kg	1.7 - 2.1
Alveolar macrophages	56.7 mg/kg	18.6 - 70.0
Epithelial lining fluid	20.7 mg/l	5 - 7
Maxillary sinus	7.5 mg/kg	2.0
Ethmoid sinus	8.2 mg/kg	2.1
Nasal polyps	9.1 mg/kg	2.6
Interstitial fluid	1.0[2] mg/l	0.8 - 1.4[2,3]
Female genital tract*	10.2[4] mg/kg	1.72[4]

* intravenous administration of a single 400 mg dose
[1] 10 h after administration
[2] unbound concentration
[3] from 3 h up to 36 h post dose
[4] at the end of infusion

Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal 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. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys.

After a 400 mg dose, recovery from urine (approximately 19% for unchanged drug, approximately 2.5% for M1, and approximately 14% for M2) and faeces (approximately 25% of unchanged drug, approximately 36% for M1, and no recovery for M2) totalled to approximately 96%.

Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

Higher plasma concentrations are observed in healthy volunteers with low body weight (such as women) and in elderly volunteers.

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).

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

Effects on the haematopoetic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys. As with other quinolones, hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs. In monkeys CNS toxicity (convulsions) occurred. These effects were seen only after treatment with high doses of moxifloxacin or after prolonged treatment.

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

Many quinolones are photoreactive and can induce phototoxic, photomutagenic and photocarcinogenic effects. In contrast, moxifloxacin was proven to be devoid of phototoxic and photogenotoxic properties when tested in a comprehensive programme of *in vitro* and *in vivo* studies. Under the same conditions other quinolones induced effects.

At high concentrations, moxifloxacin is an inhibitor of the rapid component of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT interval. Toxicological studies performed in dogs using oral doses of ≥ 90 mg/kg leading to plasma concentrations ≥ 16 mg/l caused QT prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50fold the human dose (> 300 mg/kg), leading to plasma concentrations of ≥ 200 mg/l (more than 40fold the therapeutic level), reversible, non-fatal ventricular arrhythmias were seen.

Quinolones 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 the maximum recommended therapeutic dose of 400 mg (assuming a 50 kg bodyweight) on a mg/kg basis, with plasma concentrations two to three times higher than those at the maximum therapeutic dose.

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.

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. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on a mg/kg basis with plasma concentrations in the range of the human therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate

Film coat:
Hypromellose
Macrogol 4000
Ferric oxide (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Over-labelled carton containing over-labelled blister strip of 5 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare,
Unit 4, Bradfield Road,
Ruislip, Middlesex,
HA4 0NU, UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/144/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th February 2011

10 DATE OF REVISION OF THE TEXT