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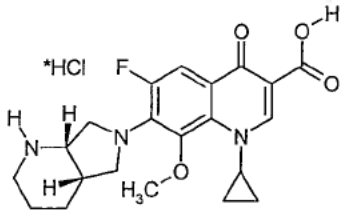
**PRODUCT INFORMATION**
**AVELOX®**
**(Moxifloxacin hydrochloride, BAYER)**

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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



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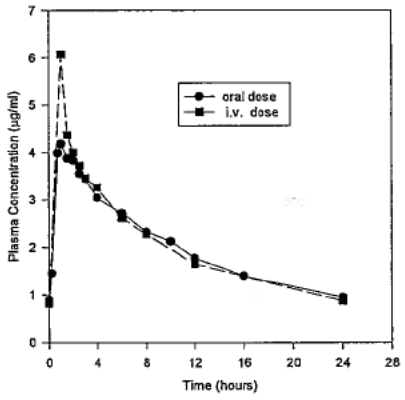
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



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Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal



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clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr}$ ≥ 30 and ≤ 60 mL/min) and severe ($Cl_{cr}$ < 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg



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or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| *Gram-positive bacteria* | *Gram-negative bacteria* | *Others* |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.



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| *Gram-positive bacteria* | *Gram-negative bacteria* | *Anaerobes* |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains) | *Klebsiella oxytoca* | *Fusobacterium spp.* |
| *Streptococcus milleri* | *Proteus mirabilis* | *Prevotella spp.* |
| *Streptococcus mitior* | *Citrobacter freundii* | *Peptostreptococcus spp.* |
| *Streptococcus agalactiae* | | |

| *Others* |
|---|
| *Legionella pneumophila* |
| *Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.



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## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | Avelox | Clarithromycin |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | Avelox | Clarithromycin |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy



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Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | Avelox | Cefuroxime axetil |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.



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The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox** (n=180) | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID** (n=187) | **Avelox** (n=315) | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID** (n=317) |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia



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- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.



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Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

**Effects on Tendons**

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

**Effects on the CNS**

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, 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 ADVERSE EFFECTS).



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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 ADVERSE 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.

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).[ECI]

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatending liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

**Skin Reactions**

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.



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**Osteomyelitis**

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).[EC2]

**Sodium content of solution for infusion**

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

**Other**

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

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.

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.[EC3]

~~INTERACTIONS WITH OTHER MEDICINES~~

~~Drugs which can affect moxifloxacin~~

~~See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.~~

~~Antacids, minerals and multi-vitamins~~

~~Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.~~

~~Anti-retroviral drugs~~

~~Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).~~



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**Drugs shown not to affect moxifloxacin**

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.



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~~Morphine~~

~~Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).~~

~~Atenolol~~

~~The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.~~

~~Theophylline~~

~~No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).~~

~~Probenecid~~

~~No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.~~

~~Antidiabetic agents~~

~~No clinically relevant interaction was seen between glibenclamide and moxifloxacin.~~

~~Use of countermeasures~~

~~Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).~~ [EC4]

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.



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**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

**Use in Lactation**

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Information for Patients**

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.



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- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

### Drugs shown not to affect moxifloxacin

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.



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Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).



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Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).[ECS]

**ADVERSE EFFECTS**

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |



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| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| **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<br>Hearing impairment including deafness (usually reversible) | |



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| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |
| **Renal and Urinary Disorders** | | | Renal impairment<br>Renal failure<br>(due to dehydration esp. in elderly with pre-existing renal disorders) | |



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| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **General Disorders and Administration Site Conditions** | Injection and infusion site reactions | Feeling unwell<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

Common: Increased gamma-glutamyl-transferase

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

**Post-Marketing Adverse Event Reports:**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia[EC6]



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## DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

**Directions to Administer**

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.



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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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C (see Presentation and Storage Conditions).**

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:
0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).



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Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m²) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

## OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

## NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA ~~LIMITED~~LTD[EC7]
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
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**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

21 December 2000

**DATE OF MOST RECENT AMENDMENT**

~~3 July 2012~~



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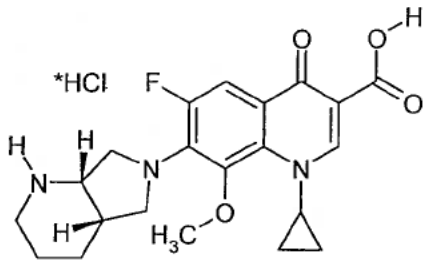
Document 1

# PRODUCT INFORMATION
# AVELOX®
# (Moxifloxacin hydrochloride, BAYER)

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

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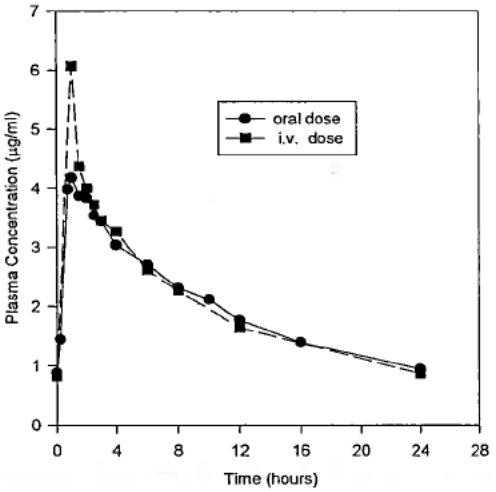
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**

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Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr}$ < 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

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or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

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| *Gram-positive bacteria* | *Gram-negative bacteria* | *Anaerobes* |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains) | *Klebsiella oxytoca* | *Fusobacterium spp.* |
| *Streptococcus milleri* | *Proteus mirabilis* | *Prevotella spp.* |
| *Streptococcus mitior* | *Citrobacter freundii* | *Peptostreptococcus spp.* |
| *Streptococcus agalactiae* | | |
| | | ***Others*** |
| | | *Legionella pneumophila* |
| | | *Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa*.

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

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## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

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Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

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The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

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- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

**Effects on Tendons**

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

**Effects on the CNS**

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, 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 ADVERSE EFFECTS).

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 ADVERSE 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.

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatending liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

**Skin Reactions**

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

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**Osteomyelitis**

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

**Sodium content of solution for infusion**

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

**Other**

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

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.

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.

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low

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relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

**Use in Lactation**

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Information for Patients**

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium),

sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).

- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

### Drugs shown not to affect moxifloxacin

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

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Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

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Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

## ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |

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| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| **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<br>Hearing impairment including deafness (usually reversible) | |
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |

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| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |
| **Renal and Urinary Disorders** | | | Renal impairment<br>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<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

Common: Increased gamma-glutamyl-transferase

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

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**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

**DOSAGE AND ADMINISTRATION**

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

**OVERDOSAGE**

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

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**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

**Directions to Administer**

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C (see Presentation and Storage Conditions).**

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

s22

16/7/14

Contact Poisons Information Centre 131126 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

## NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
®Registered Trademark of Bayer AG

## POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

## DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

## DATE OF MOST RECENT AMENDMENT

s22 [redacted]
16/7/18

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Document 2

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Document 2

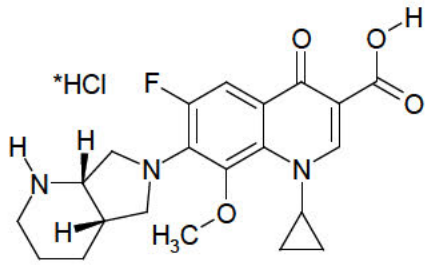
s22

Document 2

# PRODUCT INFORMATION
# AVELOX®
# (Moxifloxacin hydrochloride, BAYER)

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

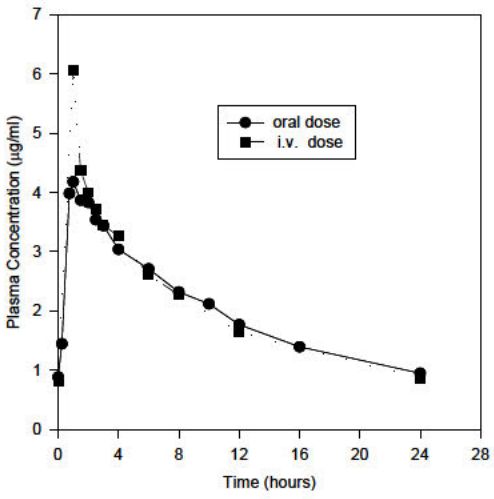
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| **Tissue or Fluid** | **Plasma Concentration** ($\mu g/mL$) | **Tissue or Fluid Concentration** ($\mu g/mL$ **or** $\mu g/g$) | **Tissue: Plasma Ratio** |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Anaerobes*** |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains)<br>*Streptococcus milleri*<br>*Streptococcus mitior*<br>*Streptococcus agalactiae* | *Klebsiella oxytoca*<br>*Proteus mirabilis*<br>*Citrobacter freundii* | *Fusobacterium spp.*<br>*Prevotella spp.*<br>*Peptostreptococcus spp.* |
| | | ***Others*** |
| | | *Legionella pneumophila*<br>*Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

**Effects on Tendons**

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

**Effects on the CNS**

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, 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~~ Avelox should be discontinued in patients experiencing symptoms of

neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

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 ADVERSE 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.

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

**Skin Reactions**

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

**Osteomyelitis**

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

**Dysglycaemia**

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

**Sodium content of solution for infusion**

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

**Other**

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

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.

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.

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to

the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

**Use in Lactation**

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Information for Patients**

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

### Drugs shown not to affect moxifloxacin

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state

during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

## ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| **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<br>Hearing impairment including deafness (usually reversible) | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |
| **Renal and Urinary Disorders** | | | Renal impairment<br>Renal failure<br>(due to dehydration esp. in elderly with pre-existing renal disorders) | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **General Disorders and Administration Site Conditions** | Injection and infusion site reactions | Feeling unwell<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

Common: Increased gamma-glutamyl-transferase

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

**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

## DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

### Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C (see Presentation and Storage Conditions).**

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

## OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

## NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
®Registered Trademark of Bayer AG

**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

21 December 2000

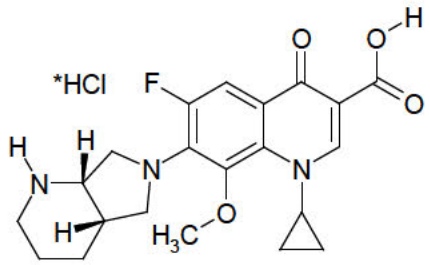
**DATE OF MOST RECENT AMENDMENT**

~~16 July 2014~~

# PRODUCT INFORMATION
# AVELOX®
# (Moxifloxacin hydrochloride, BAYER)

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

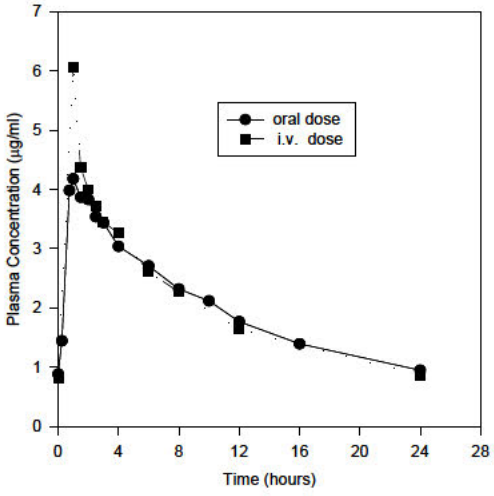
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Anaerobes*** |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains)<br>*Streptococcus milleri*<br>*Streptococcus mitior*<br>*Streptococcus agalactiae* | *Klebsiella oxytoca*<br>*Proteus mirabilis*<br>*Citrobacter freundii* | *Fusobacterium spp.*<br>*Prevotella spp.*<br>*Peptostreptococcus spp.* |
| | | ***Others*** |
| | | *Legionella pneumophila*<br>*Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

**Effects on Tendons**

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

**Effects on the CNS**

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

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 ADVERSE 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.

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

### Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

### Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

#### Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

### Sodium content of solution for infusion

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

### Other

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

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.

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.

### Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

**Use in Lactation**

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Information for Patients**

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.

- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

### Drugs shown not to affect moxifloxacin

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

## ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| **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<br>Hearing impairment including deafness (usually reversible) | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |
| **Renal and Urinary Disorders** | | | Renal impairment<br>Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders) | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **General Disorders and Administration Site Conditions** | Injection and infusion site reactions | Feeling unwell<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

Common: Increased gamma-glutamyl-transferase

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

**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

## DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

### Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C (see Presentation and Storage Conditions).**

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

## OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

## NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
®Registered Trademark of Bayer AG

**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

21 December 2000

**DATE OF MOST RECENT AMENDMENT**

s22

Document 3

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Document 3

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Document 3

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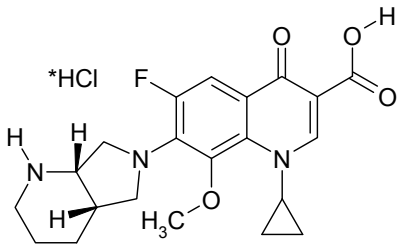
Document 3

# PRODUCT INFORMATION
# AVELOX®
# (Moxifloxacin hydrochloride, BAYER)

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

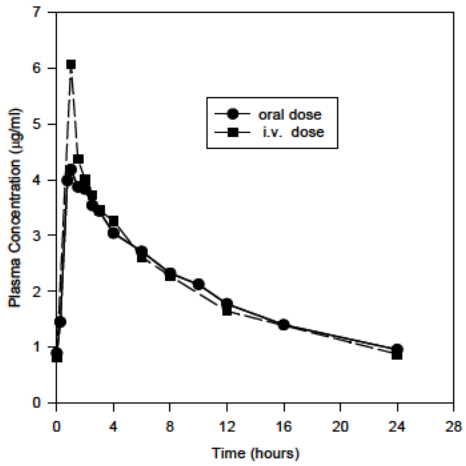
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

| *Gram-positive bacteria* | *Gram-negative bacteria* | *Anaerobes* |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains)<br>*Streptococcus milleri*<br>*Streptococcus mitior*<br>*Streptococcus agalactiae* | *Klebsiella oxytoca*<br>*Proteus mirabilis*<br>*Citrobacter freundii* | *Fusobacterium spp.*<br>*Prevotella spp.*<br>*Peptostreptococcus spp.* |

| *Others* |
|---|
| *Legionella pneumophila*<br>*Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

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

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

**Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Effects on CNS) and musculoskeletal system (see Effects on Tendons).**

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The

magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

**Effects on Tendons**

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

**Effects on the CNS**

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

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 ADVERSE 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.

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

**Skin Reactions**

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

**Osteomyelitis**

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

**Dysglycaemia**

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

**Sodium content of solution for infusion**

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

**Other**

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

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.

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.

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

### Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

**Drugs shown not to affect moxifloxacin**

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

**ADVERSE EFFECTS**

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **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<br>Hearing impairment including deafness (usually reversible) | |
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Renal and Urinary Disorders** | | | Renal impairment<br>Renal failure<br>(due to dehydration esp. in elderly with pre-existing renal disorders) | |
| **General Disorders and Administration Site Conditions** | Injection and infusion site reactions | Feeling unwell<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

Common: Increased gamma-glutamyl-transferase

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

**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

## DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

**Directions to Administer**

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous

line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).**

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

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

**OVERDOSAGE**

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

**PRESENTATION AND STORAGE CONDITIONS**

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

**NAME AND ADDRESS OF THE SPONSOR**

BAYER AUSTRALIA LTD
ABN 22 000 138 714

875 Pacific Highway
PYMBLE NSW 2073
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**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

21 December 2000

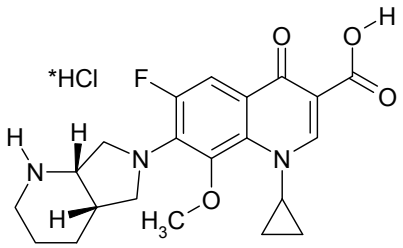
**DATE OF MOST RECENT AMENDMENT**

~~30 July 2015~~xx xxxxxxx xxxxx

# PRODUCT INFORMATION
# AVELOX®
# (Moxifloxacin hydrochloride, BAYER)

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

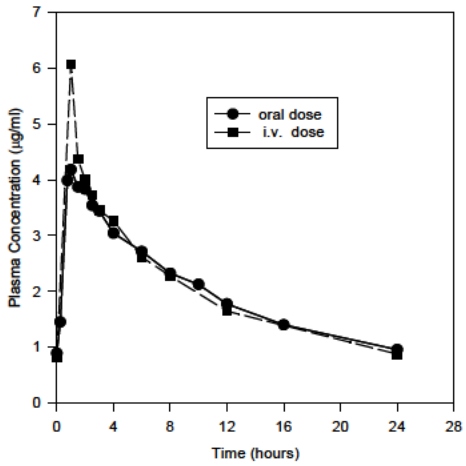
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Anaerobes*** |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains)<br>*Streptococcus milleri*<br>*Streptococcus mitior*<br>*Streptococcus agalactiae* | *Klebsiella oxytoca*<br>*Proteus mirabilis*<br>*Citrobacter freundii* | *Fusobacterium spp.*<br>*Prevotella spp.*<br>*Peptostreptococcus spp.* |
| | | ***Others*** |
| | | *Legionella pneumophila*<br>*Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

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

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

**Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Effects on CNS) and musculoskeletal system (see Effects on Tendons).**

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The

magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

**Effects on Tendons**

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

**Effects on the CNS**

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

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 ADVERSE 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.

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

### Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

### Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

### Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

### Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

#### Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

### Sodium content of solution for infusion

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

### Other

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

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.

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.

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

### Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

<u>Antacids, minerals and multi-vitamins</u>

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

**Drugs shown not to affect moxifloxacin**

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

**ADVERSE EFFECTS**

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **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<br>Hearing impairment including deafness (usually reversible) | |
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Renal and Urinary Disorders** | | | Renal impairment<br>Renal failure<br>(due to dehydration esp. in elderly with pre-existing renal disorders) | |
| **General Disorders and Administration Site Conditions** | Injection and infusion site reactions | Feeling unwell<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

Common: Increased gamma-glutamyl-transferase

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

**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

## DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

### Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).**

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

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

**OVERDOSAGE**

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

**PRESENTATION AND STORAGE CONDITIONS**

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

**NAME AND ADDRESS OF THE SPONSOR**

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**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

21 December 2000

**DATE OF MOST RECENT AMENDMENT**

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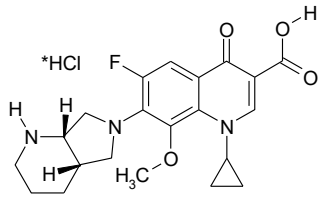
**PRODUCT INFORMATION**
**AVELOX®**
**(Moxifloxacin hydrochloride, BAYER)**

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

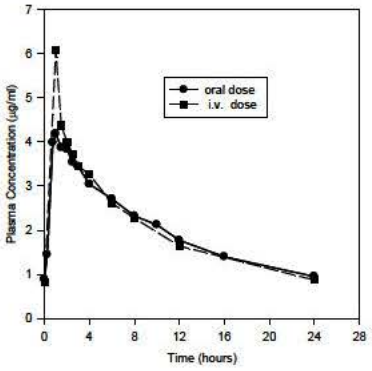
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39 3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48 0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51 8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48 2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49 3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38 0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48 2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distr bution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are

approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq 30$ and $\leq 60$ mL/min) and severe ($Cl_{cr} < 30$ mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be suscept ble to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-suscept ble strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq$ 2 µg/mL) against the following microorganisms, but their clinical significance is unknown.

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Anaerobes*** |
|---|---|---|

| | | |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains)<br>*Streptococcus milleri*<br>*Streptococcus mitior*<br>*Streptococcus agalactiae* | *Klebsiella oxytoca*<br>*Proteus mirabilis*<br>*Citrobacter freundii* | *Fusobacterium spp.*<br>*Prevotella spp.*<br>*Peptostreptococcus spp.* |
| | | ***Others*** |
| | | *Legionella pneumophila*<br>*Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the ant bacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is l kely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not l kely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

**INDICATIONS**

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by suscept ble organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

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

## CONTRAINDICATIONS

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

Commented [S21]: Term "quinolones" used as per TGA request 20 08 19 – despite CCDS editorial change to preferred term "fluoroquinolones"

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

**Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see ~~Effects on CNS~~Pyschiatric reactions) and musculoskeletal system (see ~~Effects on Tendons~~Tendonitis and tendon rupture).**

Commented [S22]: Cross references updated according to new titles in CCDS 22

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the

recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral ant bacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inh biting peristalsis are contraindicated in patients who develop serious diarrhoea.

Commented [S2B]: To keep Avelox PI aligned with CCDS and harmonise with Ciproxin PI

Tendonitis and tendon rupture~~Effects on Tendons~~

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, ~~Tendon inflammation and rupture~~ that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin. This may occur even within the first 48 hours of treatment, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased ~~particularly~~ in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. ~~and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been~~

~~reported.~~ At the first sign of tendonitis (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 Avelox should be discontinued. ~~Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.~~

Commented [S224]: Additional information as per CCDS update

Seizures ~~Effects on the CNS~~

Seizures may occur with fluoroquinolone~~quinolone~~ therapy. Avelox 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), that may predispose them to seizures or lower the seizure threshold.

Commented [S225]: Updated title and information as per CCDS update

Myasthenia gravis

Commented [S226]: New title as per CCDS update

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

Peripheral neuropathy

Commented [S227]: New title as part of CCDS update

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irrevers ble condition (see ADVERSE EFFECTS).

Psychiatric reactions

Fluoroquinolones, including moxifloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving moxifloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care. ~~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 ADVERSE 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.~~

Commented [S228]: Recommended wording from TGA actually states Ciprofloxacin here, which is not the right wording aligned to the product

Commented [S229]: Additional information requested by TGA The wording of this precaution is similar to FDA PI for Avelox

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases. 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.

Commented [S22_10]: Wording moved from the 'Other' section to be included with 'hypersensitivity reactions'

**Skin Reactions**

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

**Osteomyelitis**

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

**Dysglycaemia**

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS)

Commented [S22_11]: Additional information regarding hypoglycaemic coma requested by TGA

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

Commented [S22-12]: Additional information requested by TGA

**Sodium content of solution for infusion**

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

**Other**

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

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.

~~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.~~

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inh bition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500

mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

**Use in Lactation**

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Information for Patients**

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate,

or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).

- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

**INTERACTIONS WITH OTHER MEDICINES**

**Drugs which can affect moxifloxacin**

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

**Drugs shown not to affect moxifloxacin**

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

**ADVERSE EFFECTS**

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| **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<br>Hearing impairment including deafness (usually reversible) | |
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |
| **Renal and Urinary Disorders** | | | Renal impairment<br>Renal failure<br>(due to dehydration esp. in elderly with pre-existing renal disorders) | |
| **General Disorders and Administration Site Conditions** | Injection and infusion site reactions | Feeling unwell<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

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

**Commented [[redacted]3]:** Additional information as per CCDS 22 update

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

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very

rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions l ke Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

**DOSAGE AND ADMINISTRATION**

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |

| | | |
|---|---|---|
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

**Directions to Administer**

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).**

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

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:
0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

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.

Commented [S22.4]: Additional information as per CCDS 22 update

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

**OVERDOSAGE**

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

**PRESENTATION AND STORAGE CONDITIONS**

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30 C. Do not store below 15°C. Do not refrigerate.

**NAME AND ADDRESS OF THE SPONSOR**

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
®Registered Trademark of Bayer AG

**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG**

21 December 2000

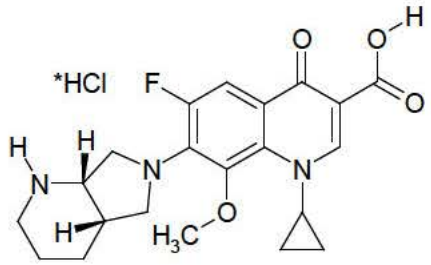
**DATE OF MOST RECENT AMENDMENT**

13 June 2019~~2 November 2017~~

# PRODUCT INFORMATION
# AVELOX®
# (Moxifloxacin hydrochloride, BAYER)

## NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:




## DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

## PHARMACOLOGY

### Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

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

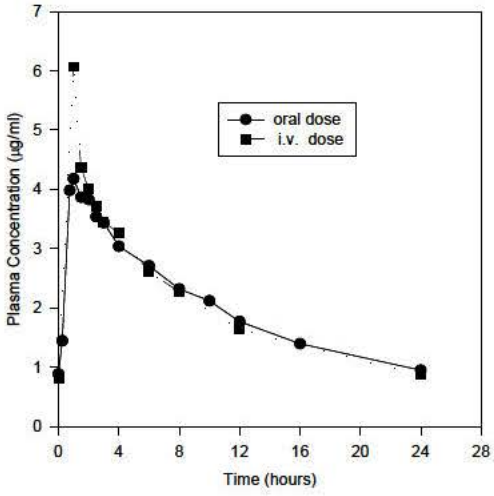
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) $C_{max}$ and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

| | $C_{max}$ (mg/L) | AUC (mg•h/L) | Half-life (hr) |
|---|---|---|---|
| Single Dose Oral | | | |
| Healthy (n = 372) | 3.1 ± 1.0 | 36.1 ± 9.1 | 11.5 - 15.6* |
| Single Dose I.V. | | | |
| Healthy young (n = 56) | 3.9 ± 0.9 | 39.3 ± 8.6 | 8.2 - 15.4* |
| Patients (n = 118) | | - | |
| Male (n = 64) | 4.4 ± 3.7 | | |
| Female (n = 54) | 4.5 ± 2.0 | | |
| < 65 years (n = 58) | 4.6 ± 4.2 | | |
| > 65 years (n = 60) | 4.3 ± 1.3 | | |
| Multiple Dose Oral | | | |
| Healthy young male/female (n = 15) | 4.5 ± 0.5 | 48.0 ± 2.7 | 12.7 ±1.9 |
| Healthy elderly male (n = 8) | 3.8 ± 0.3 | 51.8 ± 6.7 | |
| Healthy elderly female (n = 8) | 4.6 ± 0.6 | 54.6 ± 6.7 | |
| Healthy young male (n = 8) | 3.6 ± 0.5 | 48.2 ± 9.0 | |
| Healthy young female (n = 9) | 4.2 ± 0.5 | 49.3 ± 9.5 | |
| Multiple Dose I.V. | | | |
| Healthy young male (n = 8) | 4.2 ± 0.8 | 38.0 ± 4.7 | 14.8 ± 2.2 |
| Healthy elderly (n =12; 8 male, 4 female) | 6.1 ± 1.3 | 48.2 ± 0.9 | 10.1 ± 1.6 |
| Patients (n = 107) | | - | |
| Male (n = 58) | 4.2 ± 2.6 | | |
| Female (n = 49) | 4.6 ± 1.5 | | |
| < 65 years (n = 52) | 4.1 ± 1.4 | | |
| > 65 years (n = 55) | 4.7 ± 2.7 | | |

* range of means from different studies

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)**



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state ($V_{ss}$) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

**Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg**

| Tissue or Fluid | Plasma Concentration ($\mu g/mL$) | Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$) | Tissue: Plasma Ratio |
|---|---|---|---|
| **Respiratory** | | | |
| Alveolar macrophages | 3.3 ± 0.7 | 61.8 ± 27.3 | 21.2 ± 10.0 |
| Bronchial mucosa | 3.3 ± 0.7 | 5.5 ± 1.3 | 1.7 ± 0.3 |
| Epithelial lining fluid | 3.3 ± 0.7 | 24.4 ± 14.7 | 8.7 ± 6.1 |
| **Sinus** | | | |
| Maxillary sinus mucosa | 3.7 ± 1.1 | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior ethmoid mucosa | 3.7 ± 1.1 | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal polyps | 3.7 ± 1.1 | 9.8 ± 4.5 | 2.6 ± 0.6 |
| **Skin, Musculoskeletal** | | | |
| Blister fluid | 3.0 ± 0.5 | 2.6 ± 0.9 | 0.9 ± 0.2 |

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 is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are

approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, $C_{max}$ and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and $C_{max}$ were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m$^2$). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq 30$ and $\leq 60$ mL/min) and severe ($Cl_{cr} < 30$ mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

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 also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

**Microbiology**

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

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

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Others*** |
|---|---|---|
| *Streptococcus pneumoniae* (penicillin-susceptible strains) | *Haemophilus influenzae* | *Chlamydia pneumoniae* |
| *Staphylococcus aureus* (methicillin-susceptible strains) | *Haemophilus parainfluenzae* | *Mycoplasma pneumoniae* |
| *Streptococcus pyogenes (group A)* | *Klebsiella pneumoniae* | |
| | *Moraxella catarrhalis* | |
| | *Escherichia coli* | |
| | *Enterobacter cloacae* | |

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

| ***Gram-positive bacteria*** | ***Gram-negative bacteria*** | ***Anaerobes*** |
|---|---|---|

| | | |
|---|---|---|
| *Streptococcus pneumoniae* (including penicillin and macrolide resistant strains)<br>*Streptococcus milleri*<br>*Streptococcus mitior*<br>*Streptococcus agalactiae* | *Klebsiella oxytoca*<br>*Proteus mirabilis*<br>*Citrobacter freundii* | *Fusobacterium spp.*<br>*Prevotella spp.*<br>*Peptostreptococcus spp.* |
| | | ***Others*** |
| | | *Legionella pneumophila*<br>*Coxiella burnetti* |

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

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 and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

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.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following 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.

**Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

## CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

### Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0124 | 82% (271/331) | 80% (270/338) |
| Study 0127 | 89% (222/250) | 89% (224/251) |
| **Bacteriological eradication*** | | |
| *Haemophilus influenzae* | 90% (73/81) | 76% (54/84) |
| *Streptococcus pneumoniae* | 83% (48/54) | 95% (56/59) |
| *Moraxella catarrhalis* | 86% (43/50) | 98% (47/48) |

* Study 0124 and 0127 combined

### Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

| | **Avelox** | **Clarithromycin** |
|---|---|---|
| **Overall clinical response** | | |
| Study 0119 | 93% (141/152) | 92% (141/153) |
| Study 0130 | 95% (184/194) | 95% (178/188) |
| **Bacteriological eradication*** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 94% (29/31) |
| *Haemophilus influenzae* | 97% (35/36) | 81% (21/26) |
| *Moraxella catarrhalis* | 83% (10/12) | 100% (4/4) |
| *Chlamydia pneumoniae* | 92% (47/51) | 98% (48/49) |
| *Mycoplasma pneumoniae* | 96% (23/24) | 100% (20/20) |
| | **Avelox** | **Amoxycillin** |
| **Overall clinical response** | | |
| Study 0140 | 89% (143/160) | 89% (159/178) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 90% (43/48) | 85% (39/46) |
| *Haemophilus influenzae* | 100% (9/9) | 83% (15/18) |

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

**Acute bacterial sinusitis**

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

| | **Avelox** | **Cefuroxime axetil** |
|---|---|---|
| **Overall clinical response** | 86% (186/217) | 89% (198/222) |
| **Bacteriological eradication** | | |
| *Streptococcus pneumoniae* | 95% (36/38) | 100% (32/32) |
| *Haemophilus influenzae* | 100% (17/17) | 94% (15/16) |
| *Staphylococcus aureus* | 100% (14/14) | 88% (7/8) |
| *Moraxella catarrhalis* | 100% (10/10) | 100% (5/5) |

**Skin and Skin Structure Infections**

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

| | **Avelox (n=180)** | **Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)** | **Avelox (n=315)** | **Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)** |
|---|---|---|---|---|
| | Study 100273 | | Study 10279 | |
| **Overall Clinical Response** | 143/180 (79%) | 153/187 (82%) | 254/315 (81%) | 268/317 (85%) |
| Skin abscess | 42/53 (79%) | 52/56 (93%) | 92/98 (94%) | 82/93 (88%) |
| Cellulitis/erysipelas[a] | 36/43 (84%) | 38/45 (84%) | 99/110 (90%) | 105/112 (94%) |
| Diabetic foot infection | 25/37 (68%) | 25/41 (61% | 25/49 (51%) | 42/63 (67%) |
| Fasciitis | NA | NA | 11/22 (50%) | 7/13 (54%) |
| Surgical wound infection | 11/12 (92%) | 8/8 (100%) | 8/9 (89%) | 12/13 (92%) |
| Infected ischemic ulcers | 10/13 (77%) | 6/10 (60%) | 2/6 (33%) | 4/4 (100%) |
| Infection of traumatic lesion[b] | 11/12 (92%) | 10/13 (77%) | 17/21 (81%) | 16/19 (84%) |
| Other infection types[c] | 8/10 (80%) | 12/14 (86%) | NA | NA |

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

| | Study 100273 | | Study 10279 | |
|---|---|---|---|---|
| | **Avelox n/N (%)** | **Comparator n/N (%)** | **Avelox n/N (%)** | **Comparator n/N (%)** |
| *Staphylococcus aureus* | 50/64 (78%) | 47/59 (80%) | 48/59 (81%) | 71/78 (91%) |
| *Streptococcus pyogenes* | 13/18 (72%) | 8/12 (67%) | 9/15 (60%) | 8/9 (89%) |
| *Escherichia coli* | 7/8 (88%) | 11/12 (92%) | 24/30 (80%) | 16/20 (80%) |
| *Klebsiella pneumoniae* | 5/6 (83%) | 4/7 (57%) | 5/5(100%) | 2/2 (100%) |
| *Enterobacter cloacae* | 4/5 (80%) | 1/2 (50%) | 5/6 (83%) | 2/4 (50%) |

## INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

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

## CONTRAINDICATIONS

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

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

## PRECAUTIONS

**Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Pyschiatric reactions) and musculoskeletal system (see Tendonitis and tendon rupture).**

### General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

### Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the

recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). 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.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

**Antibiotic-associated Colitis**

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

**Tendonitis and tendon rupture**

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin. This may occur even within the first 48 hours of treatment, and 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 in patients with solid organ transplants. At the first sign of tendonitis (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 Avelox should be discontinued.

**Seizures**

Seizures may occur with fluoroquinolone therapy. Avelox 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), that may predispose them to seizures or lower the seizure threshold.

**Myasthenia gravis**

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

**Peripheral neuropathy**

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

**Psychiatric reactions**

Fluoroquinolones, including moxifloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving moxifloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

**Effects on ability to drive or use machinery**

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

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 ADVERSE EFFECTS).

**Paediatric Use**

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

**Patients with severe hepatic impairment**

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

**Photosensitivity Potential**

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

**Hypersensitivity Reactions**

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases. 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.

**Skin Reactions**

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

**Osteomyelitis**

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

**Dysglycaemia**

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

**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 dissection, or in presence of other risk factors or conditions

predisposing for aortic aneurysm and dissection (eg 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.

**Sodium content of solution for infusion**

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. The sodium content of the solution for infusion (250 mL) is 34 mmol.

**Other**

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

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.

**Carcinogenicity and Mutagenicity**

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

**Effects on Fertility**

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

**Use In Pregnancy (Category B3)**

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An

increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

**Use in Lactation**

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Information for Patients**

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

## INTERACTIONS WITH OTHER MEDICINES

### Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

### Drugs shown not to affect moxifloxacin

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

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters ($C_{max}$, $t_{max}$, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on 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 oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin 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.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

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.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased $C_{max}$ (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin ($C_{max}$ 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin 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%).

**ADVERSE EFFECTS**

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

| | | |
|---|---|---|
| Common | ≥ 1/100 | to < 1/10 |
| Uncommon | ≥ 1/1000 | to < 1/100 |
| Rare | ≥ 1/10000 | to < 1/1000 |
| Very rare | < 1/10000 | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Infections and Infestations** | Mycotic superinfections | | | |
| **Blood and the Lymphatic System Disorders** | | Anaemia<br>Leucopaenia(s)<br>Neutropaenia<br>Thrombocytopaenia<br>Thrombocythaemia<br>Prothrombin time prolonged/INR increased | Thromboplastin level abnormal | Prothrombin level increased/INR decreased<br>Prothrombin level/INR abnormal |
| **Immune System Disorders** | | Allergic reaction<br>Pruritis<br>Rash<br>Urticaria<br>Blood eosinophilia | Anaphylactic/ anaphylactoid reaction<br>Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening) | Anaphylactic/ anaphylactoid shock (potentially life threatening) |
| **Metabolism and Nutrition Disorders** | | Hyperlipidaemia | Hyperglycaemia<br>Hyperuricaemia | |
| **Psychiatric Disorders** | | Anxiety reactions<br>Psychomotor hyperactivity/ agitation | Emotional lability<br>Depression<br>Hallucinations | Depersonalisation<br>Psychotic reactions |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Nervous system disorders** | Headache<br>Dizziness | Par- / Dysaesthesia<br>Taste disorder (incl. ageusia in very rare cases)<br>Confusion and disorientation<br>Sleep disorder<br>Tremor<br>Vertigo<br>Somnolence | Hypoaesthesia<br>Smell disorders (incl. anosmia)<br>Abnormal dreams<br>Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo;<br>Seizures of various clinical manifestations (incl. grand mal convulsions)<br>Disturbed attention<br>Speech disorders<br>Amnesia<br>Peripheral neuropathy and polyneuropathy | Hyperaesthesia |
| **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<br>Hearing impairment including deafness (usually reversible) | |
| **Cardiovascular System Disorders** | QT prolongation in patients with hypokalaemia | QT prolongation<br>Palpitations<br>Tachycardia<br>Vasodilatation | Ventricular tachyarrhythmias<br>Syncope<br>Hypertension<br>Hypotension | Unspecified arrhythmias |
| **Respiratory, thoracic and mediastinal Disorders** | | Dyspnoea (including asthmatic conditions) | | |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Very Rare |
|---|---|---|---|---|
| **Gastrointestinal Disorders** | Nausea<br>Vomiting<br>Gastrointestinal and abdominal pains<br>Diarrhoea | Decreased appetites and food intake<br>Constipation<br>Dyspepsia<br>Flatulence<br>Gastroenteritis (excl. erosive gastroenteritis)<br>Increased amylase | Dysphagia<br>Stomatitis<br>Antibiotic associated colitis (in very rare cases associated with life threatening complications) | |
| **Hepatobiliary Disorders** | Increase in transaminases | Hepatic impairment (incl. LDH increase)<br>Increased bilirubin<br>Increased gamma-glutamyl-transferase<br>Increase in blood alkaline phosphatase | Jaundice<br>Hepatitis (predominantly cholestatic) | |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | Arthralgia<br>Myalgia | Tendonitis<br>Increased muscle tone and cramping<br>Muscular weakness | Arthritis |
| **Renal and Urinary Disorders** | | | Renal impairment<br>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<br>Unspecific pain<br>Sweating<br>Infusion site (thrombo-) phlebitis | Oedema | |

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendonitis, 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: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very

rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

**Post-Marketing Adverse Event Reports**

**Cardiovascular System Disorders:**

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

**Hepatobiliary Disorder:**

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

**Musculoskeletal, Connective Tissue and Bone Disorder:**

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

**Psychiatric Disorders:**

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

**Nervous System Disorders:**

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

**Skin and Subcutaneous Tissue Disorders:**

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

**Renal and Urinary Disorders:**

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

**Metabolism and Nutrition Disorders:**

Hypoglycaemia

**DOSAGE AND ADMINISTRATION**

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

| Infection | Daily Dose | Usual Duration |
|---|---|---|
| Acute bacterial sinusitis | 400 mg | 10 days<br>(oral therapy) |
| Acute bacterial exacerbations of chronic bronchitis | 400 mg | 5 days<br>(sequential IV/oral therapy*, oral therapy) |
| Community acquired pneumonia | 400 mg | 10 days<br>(oral therapy) |
| | 400 mg | 7 – 14 days<br>(sequential IV/oral therapy) |

| | | |
|---|---|---|
| Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection | 400 mg | 7-21 days **<br>(sequential IV/oral therapy*) |

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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

**Directions to Administer**

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

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.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).**

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

**Compatible solutions for infusion**

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:
0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

**Incompatibilities**

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

**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.

**Dose adjustments**

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m$^2$) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

## OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg 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 should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

## NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
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## POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

## DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

## DATE OF MOST RECENT AMENDMENT

13 June 2019