

1 **AVELOX[®]**
2 (moxifloxacin hydrochloride) Tablets
3 **AVELOX[®] I.V.**
4 (moxifloxacin hydrochloride in sodium chloride injection)

5 08918409, R.XX

08/08

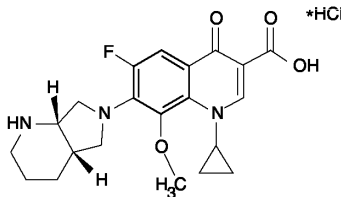
6 **WARNING:**

7 **Fluoroquinolones, including AVELOX[®], are associated with an increased risk of**
8 **tendinitis and tendon rupture in all ages. This risk is further increased in older patients**
9 **usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with**
10 **kidney, heart or lung transplants (See WARNINGS).**

11 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
12 AVELOX and other antibacterial drugs, AVELOX should be used only to treat or prevent
13 infections that are proven or strongly suspected to be caused by bacteria.

14 **DESCRIPTION**

15 AVELOX (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is
16 available as AVELOX Tablets for oral administration and as AVELOX I.V. for intravenous
17 administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of
18 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3
19 quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular
20 weight of 437.9. Its empirical formula is $C_{21}H_{24}FN_3O_4 \cdot HCl$ and its chemical structure is as
21 follows:



22 AVELOX Tablets are available as film-coated tablets containing moxifloxacin hydrochloride
23 (equivalent to 400 mg moxifloxacin). The inactive ingredients are microcrystalline cellulose,
24 lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium
25 dioxide, polyethylene glycol and ferric oxide.

26 AVELOX I.V. is available in ready-to-use 250 mL latex-free flexibags as a sterile, preservative free,
27 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg
28 moxifloxacin) with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is
29 yellow. The color does not affect, nor is it indicative of, product stability. The inactive
30 ingredients are sodium chloride, USP, Water for Injection, USP, and may include hydrochloric
31 acid and/or sodium hydroxide for pH adjustment.

32 **CLINICAL PHARMACOLOGY**

33 **Absorption**

34 Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The
35

36 absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a
37 high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin.
38 Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate
39 of systemic absorption (AUC).
40 The mean (\pm SD) C_{max} and AUC values following single and multiple doses of 400 mg
41 moxifloxacin given orally are summarized below.

	C_{max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose Oral Healthy (n = 372)	3.1 \pm 1.0	36.1 \pm 9.1	11.5 - 15.6*
Multiple Dose Oral Healthy young male/female (n = 15)	4.5 \pm 0.5	48 \pm 2.7	12.7 \pm 1.9
Healthy elderly male (n = 8)	3.8 \pm 0.3	51.8 \pm 6.7	
Healthy elderly female (n = 8)	4.6 \pm 0.6	54.6 \pm 6.7	
Healthy young male (n = 8)	3.6 \pm 0.5	48.2 \pm 9	
Healthy young female (n = 9)	4.2 \pm 0.5	49.3 \pm 9.5	

42 * Range of means from different studies

43 The mean (\pm SD) C_{max} and AUC values following single and multiple doses of 400 mg
44 moxifloxacin given by 1 hour I.V. infusion are summarized below.

	C_{max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose I.V. Healthy young male/female (n = 56)	3.9 \pm 0.9	39.3 \pm 8.6	8.2 - 15.4*
Patients (n = 118)			
Male (n = 64)	4.4 \pm 3.7		
Female (n = 54)	4.5 \pm 2		
< 65 years (n = 58)	4.6 \pm 4.2		
\geq 65 years (n = 60)	4.3 \pm 1.3		
Multiple Dose I.V. Healthy young male (n = 8)	4.2 \pm 0.8	38 \pm 4.7	14.8 \pm 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 \pm 1.3	48.2 \pm 0.9	10.1 \pm 1.6
Patients** (n = 107)			
Male (n = 58)	4.2 \pm 2.6		
Female (n = 49)	4.6 \pm 1.5		
< 65 years (n = 52)	4.1 \pm 1.4		
\geq 65 years (n = 55)	4.7 \pm 2.7		

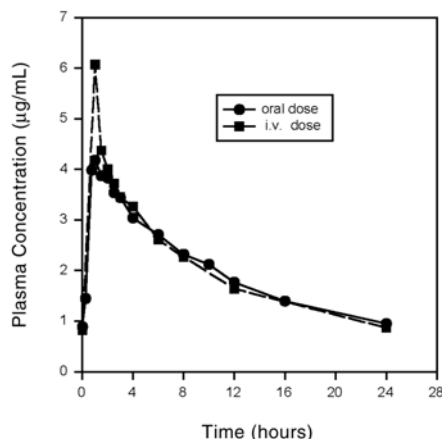
45 * Range of means from different studies

46 ** Expected C_{max} (concentration obtained around the time of the end of the infusion)

47 Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg
48 single oral dose). The mean (\pm SD) elimination half-life from plasma is 12 \pm 1.3 hours; steady-state

49 is achieved after at least three days with a 400 mg once daily regimen.

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



52

53 **Distribution**

54 Moxifloxacin is approximately 30-50% bound to serum proteins, independent of drug
55 concentration. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg.
56 Moxifloxacin is widely distributed throughout the body, with tissue concentrations often
57 exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and
58 bronchial secretions, mucosa of the sinuses, skin blister fluid, subcutaneous tissue, skeletal muscle,
59 and abdominal tissues and fluids following oral or intravenous administration of 400 mg.
60 Moxifloxacin concentrations measured post-dose in various tissues and fluids following a 400 mg
61 oral or I.V. dose are summarized in the following table. The rates of elimination of moxifloxacin
62 from tissues generally parallel the elimination from plasma.

63 **Moxifloxacin Concentrations (mean ± SD) in Tissues**
64 **and the Corresponding Plasma Concentrations After a Single 400 mg Oral or**
65 **Intravenous Dose[§]**

Tissue or Fluid	N	Plasma Concentration (µg/mL)	Tissue or Fluid Concentration (µg/mL or µg/g)	Tissue Plasma Ratio:
Respiratory				
Alveolar Macrophages	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10
Bronchial Mucosa	8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial Lining Fluid	5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus				
Maxillary Sinus Mucosa	4	3.7 ± 1.1 [†]	7.6 ± 1.7	2 ± 0.3
Anterior Ethmoid Mucosa	3	3.7 ± 1.1 [†]	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	3.7 ± 1.1 [†]	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal				

Blister Fluid	5	3.0 ± 0.5 [†]	2.6 ± 0.9	0.9 ± 0.2
Subcutaneous Tissue	6	2.3 ± 0.4 [#]	0.9 ± 0.3*	0.4 ± 0.6
Skeletal Muscle	6	2.3 ± 0.4 [#]	0.9 ± 0.2*	0.4 ± 0.1
Intra-Abdominal				
Abdominal tissue	8	2.9 ± 0.5	7.6 ± 2.0	2.7 ± 0.8
Abdominal exudate	10	2.3 ± 0.5	3.5 ± 1.2	1.6 ± 0.7
Abscess fluid	6	2.7 ± 0.7	2.3 ± 1.5	0.8 ± 0.4

66 [§]all moxifloxacin concentrations were measured 3 hours after a single 400 mg dose, except the
 67 abdominal tissue and exudate concentrations which were measured at 2 hours post-dose and
 68 the sinus concentrations which were measured 3 hours post-dose after 5 days of dosing.

69 [†] N = 5

70 [‡] N = 7

71 [#] N = 12

72 * Reflects only non-protein bound concentrations of drug.

73 **Metabolism**

74 Approximately 52% of an oral or intravenous dose of moxifloxacin is metabolized via
 75 glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in
 76 moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1)
 77 accounts for approximately 38% of the dose, and is eliminated primarily in the feces.
 78 Approximately 14% of an oral or intravenous dose is converted to a glucuronide conjugate
 79 (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are
 80 approximately 40% those of the parent drug, while plasma concentrations of M1 are generally
 81 less than 10% those of moxifloxacin.

82 *In vitro* studies with cytochrome (CYP) P450 enzymes indicate that moxifloxacin does not inhibit
 83 CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to
 84 alter the pharmacokinetics of drugs metabolized by these enzymes.

85 **Excretion**

86 Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged
 87 drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as
 88 either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance
 89 and renal clearance are 12 ± 2 L/hr and 2.6 ± 0.5 L/hr, respectively.

90 **Special Populations**

91 **Geriatric**

92 Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female)
 93 and 17 young (8 male; 9 female) healthy volunteers, there were no age-related changes in
 94 moxifloxacin pharmacokinetics. In 16 healthy male volunteers (8 young; 8 elderly) given a
 95 single 200 mg dose of oral moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was
 96 not statistically different between young and elderly males and elimination half-life was
 97 unchanged. No dosage adjustment is necessary based on age. In large phase III studies, the
 98 concentrations around the time of the end of the infusion in elderly patients following
 99 intravenous infusion of 400 mg were similar to those observed in young patients.

100 **Pediatric**

101 The pharmacokinetics of moxifloxacin in pediatric subjects have not been studied.

102 **Gender**

103 Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males
104 (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16%
105 higher, respectively, in females compared to males. There are no significant differences in
106 moxifloxacin pharmacokinetics between male and female subjects when differences in body
107 weight are taken into consideration.

108 A 400 mg single dose study was conducted in 18 young males and females. The comparison of
109 moxifloxacin pharmacokinetics in this study (9 young females and 9 young males) showed no
110 differences in AUC or C_{max} due to gender. Dosage adjustments based on gender are not necessary.

111 **Race**

112 Steady-state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those
113 determined in Caucasians, with a mean C_{max} of 4.1 $\mu\text{g/mL}$, an AUC_{24} of 47 $\mu\text{g}\cdot\text{h/mL}$, and an
114 elimination half-life of 14 hours, following 400 mg p.o. daily.

115 **Renal Insufficiency**

116 The pharmacokinetic parameters of moxifloxacin are not significantly altered in mild, moderate,
117 severe, or end-stage renal disease. No dosage adjustment is necessary in patients with renal
118 impairment, including those patients requiring hemodialysis (HD) or continuous ambulatory
119 peritoneal dialysis (CAPD).

120 In a single oral dose study of 24 patients with varying degrees of renal function from normal to
121 severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin were reduced by 21%
122 and 28% in the patients with moderate ($\text{CL}_{CR} \geq 30$ and ≤ 60 mL/min) and severe ($\text{CL}_{CR} < 30$
123 mL/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients
124 was increased by 13%. In the moderate and severe renally impaired patients, the mean AUC for
125 the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and
126 C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and
127 1.4-fold (ranging up to 2.5-fold), respectively.

128 The pharmacokinetics of single dose and multiple dose moxifloxacin were studied in patients with
129 $\text{CL}_{CR} < 20$ mL/min on either hemodialysis or continuous ambulatory peritoneal dialysis (8 HD, 8
130 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin in these HD and CAPD
131 patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of
132 moxifloxacin were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared
133 to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to
134 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of
135 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5 to 3,
136 compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin are not
137 microbiologically active, and the clinical implication of increased exposure to these metabolites in
138 patients with renal disease including those undergoing HD and CAPD has not been studied.

139 Oral administration of 400 mg QD moxifloxacin for 7 days to patients on HD or CAPD produced
140 mean systemic exposure (AUC_{ss}) to moxifloxacin similar to that generally seen in healthy
141 volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable
142 between CAPD patients and healthy volunteers. Both HD and CAPD removed only small
143 amounts of moxifloxacin from the body (approximately 9% by HD, and 3% by CAPD). HD and
144 CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

145 **Hepatic Insufficiency**

146 In 400 mg single oral dose studies in 6 patients with mild (Child Pugh Class A), and 10 patients
147 with moderate (Child Pugh Class B), hepatic insufficiency, moxifloxacin mean systemic
148 exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak
149 concentration (C_{max}) was 79% and 84% of controls.

150 The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to
151 5.9-fold) and 5.7-fold (ranging up to 8-fold) in the mild and moderate groups, respectively. The mean
152 C_{max} of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and 3.9-fold). The
153 mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to
154 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and
155 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide
156 conjugates has not been studied. No dosage adjustment is recommended for mild or moderate
157 hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in severe
158 hepatic insufficiency (Child Pugh Class C) have not been studied. (See **DOSAGE AND**
159 **ADMINISTRATION.**)

160 **Photosensitivity Potential**

161 A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32
162 healthy volunteers (8 per group) demonstrated that moxifloxacin does not show phototoxicity in
163 comparison to placebo. The minimum erythematous dose (MED) was measured before and after
164 treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or
165 placebo. In this study, the MED measured for both doses of moxifloxacin were not significantly
166 different from placebo, while lomefloxacin significantly lowered the MED. (See
167 **PRECAUTIONS, Information for Patients.**)

168 It is difficult to ascribe relative photosensitivity/phototoxicity among various fluoroquinolones
169 during actual patient use because other factors play a role in determining a subject's
170 susceptibility to this adverse event such as: a patient's skin pigmentation, frequency and
171 duration of sun and artificial ultraviolet light (UV) exposure, wearing of sunscreen and protective
172 clothing, the use of other concomitant drugs and the dosage and duration of fluoroquinolone
173 therapy (See **ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-Marketing**
174 **Adverse Event Reports.**)

175 **Drug-drug Interactions**

176 The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole,
177 theophylline, warfarin, digoxin, atenolol, probenecid, morphine, oral contraceptives, ranitidine,
178 glyburide, calcium, iron, and antacids has been evaluated. There was no clinically significant
179 effect of moxifloxacin on itraconazole, theophylline, warfarin, digoxin, atenolol, oral
180 contraceptives, or glyburide kinetics. Itraconazole, theophylline, warfarin, digoxin, probenecid,
181 morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of
182 moxifloxacin. These results and the data from *in vitro* studies suggest that moxifloxacin is
183 unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4,
184 CYP2D6, CYP2C9, CYP2C19, or CYP1A2 enzymes.

185 As with all other quinolones, iron and antacids significantly reduced bioavailability of
186 moxifloxacin.

187 **Itraconazole:** In a study involving 11 healthy volunteers, there was no significant effect of
188 itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the
189 pharmacokinetics of moxifloxacin (a single 400 mg dose given on the 7th day of itraconazole
190 dosing). In addition, moxifloxacin was shown not to affect the pharmacokinetics of itraconazole.

191 **Theophylline:** No significant effect of moxifloxacin (200 mg every twelve hours for 3 days) on the
192 pharmacokinetics of theophylline (400 mg every twelve hours for 3 days) was detected in a study
193 involving 12 healthy volunteers. In addition, theophylline was not shown to affect the
194 pharmacokinetics of moxifloxacin. The effect of co-administration of a 400 mg dose of moxifloxacin
195 with theophylline has not been studied, but it is not expected to be clinically significant based on *in*
196 *vitro* metabolic data showing that moxifloxacin does not inhibit the CYP1A2 isoenzyme.

197 **Warfarin:** No significant effect of moxifloxacin (400 mg once daily for eight days) on the
198 pharmacokinetics of R- and S-warfarin (25 mg single dose of warfarin sodium on the fifth day)
199 was detected in a study involving 24 healthy volunteers. No significant change in prothrombin
200 time was observed. (See **PRECAUTIONS, Drug Interactions.**)

201 **Digoxin:** No significant effect of moxifloxacin (400 mg once daily for two days) on digoxin (0.6
202 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The mean
203 digoxin C_{max} increased by about 50% during the distribution phase of digoxin. This transient
204 increase in digoxin C_{max} is not viewed to be clinically significant. Moxifloxacin
205 pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for
206 moxifloxacin or digoxin is required when these drugs are administered concomitantly.

207 **Atenolol:** In a crossover study involving 24 healthy volunteers (12 male; 12 female), the mean
208 atenolol AUC following a single oral dose of 50 mg atenolol with placebo was similar to that
209 observed when atenolol was given concomitantly with a single 400 mg oral dose of moxifloxacin.
210 The mean C_{max} of single dose atenolol decreased by about 10% following co-administration with
211 a single dose of moxifloxacin.

212 **Morphine:** No significant effect of morphine sulfate (a single 10 mg intramuscular dose) on the
213 mean AUC and C_{max} of moxifloxacin (400 mg single dose) was observed in a study of 20 healthy
214 male and female volunteers.

215 **Oral Contraceptives:** A placebo-controlled study in 29 healthy female subjects showed that
216 moxifloxacin 400 mg daily for 7 days did not interfere with the hormonal suppression of oral
217 contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum
218 progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered
219 contraceptive agents.

220 **Probenecid:** Probenecid (500 mg twice daily for two days) did not alter the renal clearance and total
221 amount of moxifloxacin (400 mg single dose) excreted renally in a study of 12 healthy volunteers.

222 **Ranitidine:** No significant effect of ranitidine (150 mg twice daily for three days as
223 pretreatment) on the pharmacokinetics of moxifloxacin (400 mg single dose) was detected in a
224 study involving 10 healthy volunteers.

225 **Antidiabetic agents:** In diabetics, glyburide (2.5 mg once daily for two weeks pretreatment and
226 for five days concurrently) mean AUC and C_{max} were 12% and 21% lower, respectively, when
227 taken with moxifloxacin (400 mg once daily for five days) in comparison to placebo. Nonetheless,
228 blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin in
229 comparison to those taking glyburide alone, suggesting no interference by moxifloxacin on the
230 activity of glyburide. These interaction results are not viewed as clinically significant.

231 **Calcium:** Twelve healthy volunteers were administered concomitant moxifloxacin (single 400
232 mg dose) and calcium (single dose of 500 mg Ca⁺⁺ dietary supplement) followed by an additional
233 two doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no
234 significant effect on the mean AUC of moxifloxacin. The mean C_{max} was slightly reduced and the

235 time to maximum plasma concentration was prolonged when moxifloxacin was given with
236 calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours). These
237 differences are not considered to be clinically significant.

238 **Antacids:** When moxifloxacin (single 400 mg tablet dose) was administered two hours before,
239 concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum
240 hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there
241 was a 26%, 60% and 23% reduction in the mean AUC of moxifloxacin, respectively. Moxifloxacin
242 should be taken at least 4 hours before or 8 hours after antacids containing magnesium or
243 aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with
244 zinc, or VIDEX[®] (didanosine) chewable/ buffered tablets or the pediatric powder for oral solution.
245 (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND ADMINISTRATION.**)

246 **Iron:** When moxifloxacin tablets were administered concomitantly with iron (ferrous sulfate 100 mg
247 once daily for two days), the mean AUC and C_{max} of moxifloxacin was reduced by 39% and 59%,
248 respectively. Moxifloxacin should only be taken more than 4 hours before or 8 hours after iron products.
249 (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND ADMINISTRATION.**)

250 **Electrocardiogram:** Prolongation of the QT interval in the ECG has been observed in some
251 patients receiving moxifloxacin. Following oral dosing with 400 mg of moxifloxacin the mean (\pm
252 SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6
253 msec (\pm 26) (n = 787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion
254 each day) the mean change in QTc from the Day 1 pre-dose value was 9 msec (\pm 24) on Day 1 (n =
255 69) and 3 msec (\pm 29) on Day 3 (n = 290). (See **WARNINGS.**)

256 There is limited information available on the potential for a pharmacodynamic interaction in
257 humans between moxifloxacin and other drugs that prolong the QTc interval of the
258 electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the
259 QTc interval when combined with high doses of intravenous (I.V.) moxifloxacin in dogs.
260 Therefore, moxifloxacin should be avoided with Class IA and Class III antiarrhythmics. (See
261 **ANIMAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS.**)

262 MICROBIOLOGY

263 Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative
264 microorganisms. The bactericidal action of moxifloxacin results from inhibition of the
265 topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication,
266 transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to
267 enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to
268 the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents
269 active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

270 The mechanism of action for quinolones, including moxifloxacin, is different from that of
271 macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant
272 to these classes of drugs may be susceptible to moxifloxacin and other quinolones. There is no
273 known cross-resistance between moxifloxacin and other classes of antimicrobials.

274 *In vitro* resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to
275 moxifloxacin occurs *in vitro* at a general frequency of between 1.8×10^{-9} to $< 1 \times 10^{-11}$ for
276 Gram-positive bacteria.

277 Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against
278 Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may,
279 however, still be susceptible to moxifloxacin.

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

282 **Aerobic Gram-positive microorganisms**

- 283 *Enterococcus faecalis* (many strains are only moderately susceptible)
284 *Staphylococcus aureus* (methicillin-susceptible strains only)
285 *Streptococcus anginosus*
286 *Streptococcus constellatus*
287 *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]*)
288 *Streptococcus pyogenes*

289 * MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known
290 as PRSP (Penicillin-resistant *S. pneumoniae*), and are strains resistant to two or more of the
291 following antibiotics: penicillin (MIC $\geq 2 \mu\text{g/mL}$), 2nd generation cephalosporins (e.g.,
292 cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

293 **Aerobic Gram-negative microorganisms**

- 294 *Enterobacter cloacae*
295 *Escherichia coli*
296 *Haemophilus influenzae*
297 *Haemophilus parainfluenzae*
298 *Klebsiella pneumoniae*
299 *Moraxella catarrhalis*
300 *Proteus mirabilis*

301 **Anaerobic microorganisms**

- 302 *Bacteroides fragilis*
303 *Bacteroides thetaiotaomicron*
304 *Clostridium perfringens*
305 *Peptostreptococcus* species

306 **Other microorganisms**

- 307 *Chlamydia pneumoniae*
308 *Mycoplasma pneumoniae*

309 The following *in vitro* data are available, **but their clinical significance is unknown.**
310 Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 $\mu\text{g/mL}$ or less
311 against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and
312 effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not
313 been established in adequate and well-controlled clinical trials.

314 **Aerobic Gram-positive microorganisms**

- 315 *Staphylococcus epidermidis* (methicillin-susceptible strains only)
316 *Streptococcus agalactiae*
317 *Streptococcus viridans* group

318 **Aerobic Gram-negative microorganisms**

- 319 *Citrobacter freundii*
320 *Klebsiella oxytoca*
321 *Legionella pneumophila*

322 **Anaerobic microorganisms**

- 323 *Fusobacterium* species

324 *Prevotella* species

325 **Susceptibility Tests**

326 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimum
327 inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria
328 to antimicrobial compounds. The MICs should be determined using a standardized procedure.
329 Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with
330 standardized inoculum concentrations and standardized concentrations of moxifloxacin powder.
331 The MIC values should be interpreted according to the following criteria:

332 For testing Enterobacteriaceae and methicillin-susceptible *Staphylococcus aureus*:

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

337 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^a:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

340 ^aThis interpretive standard is applicable only to broth microdilution susceptibility tests with
341 *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium¹.

342 The current absence of data on resistant strains precludes defining any results other than
343 “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible” category should be
344 submitted to a reference laboratory for further testing.

345 For testing *Streptococcus* species including *Streptococcus pneumoniae*^b and *Enterococcus*
346 *faecalis*:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

351 ^bThese interpretive standards are applicable only to broth microdilution susceptibility tests using
352 cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

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

363 Standardized susceptibility test procedures require the use of laboratory control microorganisms
364 to control the technical aspects of the laboratory procedures. Standard moxifloxacin powder
365 should provide the following MIC values:

Microorganism	MIC (µg/mL)
<i>Enterococcus faecalis</i> ATCC 29212	0.06 - 0.5

368	<i>Escherichia coli</i>	ATCC 25922	0.008 - 0.06
369	<i>Haemophilus influenzae</i>	ATCC 49247 ^c	0.008 - 0.03
370	<i>Staphylococcus aureus</i>	ATCC 29213	0.015 - 0.06
371	<i>Streptococcus pneumoniae</i>	ATCC 49619 ^d	0.06 - 0.25

372 ^cThis quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth
 373 microdilution procedure using *Haemophilus* Test Medium (HTM)¹.

374 ^dThis quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth
 375 microdilution procedure using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse
 376 blood.

377 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters
 378 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.
 379 One such standardized procedure² requires the use of standardized inoculum concentrations. This
 380 procedure uses paper disks impregnated with 5-μg moxifloxacin to test the susceptibility of
 381 microorganisms to moxifloxacin.

382 Reports from the laboratory providing results of the standard single-disk susceptibility test with a
 383 5-μg moxifloxacin disk should be interpreted according to the following criteria:

384 The following zone diameter interpretive criteria should be used for testing Enterobacteriaceae
 385 and methicillin-susceptible *Staphylococcus aureus*:

386	Zone Diameter (mm)	Interpretation
387	≥ 19	Susceptible (S)
388	16 – 18	Intermediate (I)
389	≤ 15	Resistant (R)

390 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^e:

391	Zone Diameter (mm)	Interpretation
392	≥ 18	Susceptible (S)

393 ^e This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and
 394 *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)².

395 The current absence of data on resistant strains precludes defining any results other than
 396 “Susceptible”. Strains yielding zone diameter results suggestive of a “nonsusceptible” category
 397 should be submitted to a reference laboratory for further testing.

398 For testing *Streptococcus* species including *Streptococcus pneumoniae*^f and *Enterococcus*
 399 *faecalis*:

400	Zone Diameter (mm)	Interpretation
401	≥ 18	Susceptible (S)
402	15 – 17	Intermediate (I)
403	≤ 14	Resistant (R)

404 ^fThese interpretive standards are applicable only to disk diffusion tests using Mueller-Hinton
 405 agar supplemented with 5% sheep blood incubated in 5% CO₂.

406 Interpretation should be as stated above for results using dilution techniques. Interpretation
 407 involves correlation of the diameter obtained in the disk test with the MIC for moxifloxacin.

408 As with standardized dilution techniques, diffusion methods require the use of laboratory control
 409 microorganisms that are used to control the technical aspects of the laboratory procedures. For the
 410 diffusion technique, the 5-μg moxifloxacin disk should provide the following zone diameters in
 411 these laboratory test quality control strains:

412	Microorganism	Zone Diameter (mm)
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413	<i>Escherichia coli</i>	ATCC 25922	28 – 35
414	<i>Haemophilus influenzae</i>	ATCC 49247 ^g	31 – 39
415	<i>Staphylococcus aureus</i>	ATCC 25923	28 – 35
416	<i>Streptococcus pneumoniae</i>	ATCC 49619 ^h	25 – 31

417 ^g These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using
418 *Haemophilus* Test Medium (HTM)².

419 ^h These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC
420 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5%
421 sheep blood and incubated in 5% CO₂.

422 **Anaerobic Techniques:** For anaerobic bacteria, the susceptibility to moxifloxacin as MICs
423 can be determined by standardized procedures³ such as reference agar dilution methods¹. The
424 MICs obtained should be interpreted according to the following criteria:

425	MIC (ug/mL)	Interpretation
426	≤ 2	Susceptible (S)
427	4	Intermediate (I)
428	≥ 8	Resistant (R)

429 ⁱ This interpretive standard is applicable to reference agar dilution susceptibility tests using
430 *Brucella* agar supplemented with hemin, vitamin K₁ and 5% laked sheep blood.

431 Acceptable ranges of MICs (ug/mL) for control strains for reference agar dilution testing¹:

Microorganism	MIC (ug/mL)
<i>Bacteroides fragilis</i>	ATCC 25285 0.12-0.5
<i>Bacteroides thetaiotaomicron</i>	ATCC 29741 1-4
<i>Eubacterium lentum</i>	ATCC 43055 0.12-0.5

432 ^j These quality control ranges are applicable to reference agar dilution tests using *Brucella* agar
433 supplemented with hemin, vitamin K₁ and 5% laked sheep blood.

434 INDICATIONS AND USAGE

435 AVELOX Tablets and I.V. are indicated for the treatment of adults (≥ 18 years of age) with
436 infections caused by susceptible strains of the designated microorganisms in the conditions listed
437 below. (See **DOSAGE AND ADMINISTRATION** for specific recommendations. In addition, for
438 I.V. use see **PRECAUTIONS, Geriatric Use.**)

439 **Acute Bacterial Sinusitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or
440 *Moraxella catarrhalis*.

441 **Acute Bacterial Exacerbation of Chronic Bronchitis** caused by *Streptococcus*
442 *pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*,
443 methicillin-susceptible *Staphylococcus aureus*, or *Moraxella catarrhalis*.

444 **Community Acquired Pneumonia** caused by *Streptococcus pneumoniae* (including multi-drug
445 resistant strains*), *Haemophilus influenzae*, *Moraxella catarrhalis*, methicillin-susceptible
446 *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia*
447 *pneumoniae*.

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

452 **Uncomplicated Skin and Skin Structure Infections** caused by methicillin-susceptible
453 *Staphylococcus aureus* or *Streptococcus pyogenes*.

454 **Complicated Intra-Abdominal Infections** including polymicrobial infections such as
455 abscess caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus*
456 *constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides*
457 *thetaiotaomicron*, or *Peptostreptococcus* species.

458 **Complicated Skin and Skin Structure Infections** caused by methicillin-susceptible
459 *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae*
460 (See **Clinical Studies**).

461 Appropriate culture and susceptibility tests should be performed before treatment in order to isolate
462 and identify organisms causing infection and to determine their susceptibility to moxifloxacin.
463 Therapy with AVELOX may be initiated before results of these tests are known; once results
464 become available, appropriate therapy should be continued.

465 To reduce the development of drug-resistant bacteria and maintain the effectiveness of AVELOX
466 and other antibacterial drugs, AVELOX should be used only to treat or prevent infections that are
467 proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility
468 information are available, they should be considered in selecting or modifying antibacterial therapy.
469 In the absence of such data, local epidemiology and susceptibility patterns may contribute to the
470 empiric selection of therapy.

471 **CONTRAINDICATIONS**

472 Moxifloxacin is contraindicated in persons with a history of hypersensitivity to moxifloxacin or
473 any member of the quinolone class of antimicrobial agents.

474 **WARNINGS**

475 **Tendinopathy and Tendon Rupture:** Fluoroquinolones, including AVELOX, are
476 associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse
477 reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon
478 may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder),
479 the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of
480 developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in
481 older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in
482 patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid
483 use, that may independently increase the risk of tendon rupture include strenuous physical
484 activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis
485 and tendon rupture have also occurred in patients taking fluoroquinolones who do not have
486 the above risk factors. Tendon rupture can occur during or after completion of therapy; cases
487 occurring up to several months after completion of therapy have been reported. AVELOX
488 should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a
489 tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and
490 to contact their healthcare provider regarding changing to a non-quinolone antimicrobial
491 drug.

492 **THE SAFETY AND EFFECTIVENESS OF MOXIFLOXACIN IN PEDIATRIC**
493 **PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN,**
494 **AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE**
495 **PRECAUTIONS-PEDIATRIC USE, PREGNANCY AND NURSING MOTHERS**

496 **SUBSECTIONS.)**

497 **QT prolongation:** Moxifloxacin has been shown to prolong the QT interval of the
498 electrocardiogram in some patients. The drug should be avoided in patients with known
499 prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving
500 Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic
501 agents, due to the lack of clinical experience with the drug in these patient populations.
502 Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such
503 as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed.
504 An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be
505 exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials,
506 the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator
507 treated patients who received concomitant therapy with drugs known to prolong the QTc interval.
508 Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such
509 as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT
510 prolongation may increase with increasing concentrations of the drug or increasing rates of
511 infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should
512 not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias
513 including torsades de pointes. No cardiovascular morbidity or mortality attributable to QTc
514 prolongation occurred with moxifloxacin treatment in over 9,200 patients in controlled clinical
515 studies, including 223 patients who were hypokalemic at the start of treatment, and there was no
516 increase in mortality in over 18,000 moxifloxacin tablet treated patients in a post-marketing
517 observational study in which ECGs were not performed. (See **CLINICAL PHARMACOLOGY,**
518 **Electrocardiogram.** For I.V. use, see **DOSAGE AND ADMINISTRATION** and
519 **PRECAUTIONS, Geriatric Use.**)
520 The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological
521 examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage.
522 Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other
523 signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY.**)
524 Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central
525 nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression,
526 and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these
527 reactions occur in patients receiving moxifloxacin, the drug should be discontinued and appropriate
528 measures instituted. As with all quinolones, moxifloxacin should be used with caution in patients
529 with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the
530 presence of other risk factors that may predispose to seizures or lower the seizure threshold. (See
531 **PRECAUTIONS: General, Information for Patients,** and **ADVERSE REACTIONS.**)
532 **Hypersensitivity reactions:** Serious anaphylactic reactions, some following the first dose,
533 have been reported in patients receiving quinolone therapy, including moxifloxacin. Some
534 reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling,
535 pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions
536 require immediate emergency treatment with epinephrine. Moxifloxacin should be discontinued
537 at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous
538 steroids, and airway management, including intubation, may be administered as indicated.
539 Other serious and sometimes fatal events, some due to hypersensitivity, and some due to
540 uncertain etiology, have been reported rarely in patients receiving therapy with quinolones,

541 including AVELOX. These events may be severe and generally occur following the
542 administration of multiple doses. Clinical manifestations may include one or more of the
543 following:

- 544 • fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis,
545 Stevens-Johnson syndrome);
- 546 • vasculitis; arthralgia; myalgia; serum sickness;
- 547 • allergic pneumonitis;
- 548 • interstitial nephritis; acute renal insufficiency or failure;
- 549 • hepatitis; jaundice; acute hepatic necrosis or failure;
- 550 • anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic
551 thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other
552 hematologic abnormalities.

553 The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or
554 any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS:**
555 **Information for Patients** and **ADVERSE REACTIONS**).

556 *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all
557 antibacterial agents, including AVELOX, and may range in severity from mild diarrhea to
558 fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to
559 overgrowth of *C. difficile*.

560 *C. difficile* produces toxins A and B which contribute to the development of CDAD.
561 Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these
562 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must
563 be considered in all patients who present with diarrhea following antibiotic use. Careful
564 medical history is necessary since CDAD has been reported to occur over two months after
565 the administration of antibacterial agents.

566 If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile*
567 may need to be discontinued. Appropriate fluid and electrolyte management, protein
568 supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be
569 instituted as clinically indicated.

570 **Peripheral neuropathy:** Rare cases of sensory or sensorimotor axonal polyneuropathy
571 affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and
572 weakness have been reported in patients receiving quinolones.

573 **PRECAUTIONS**

574 **General:** Quinolones may cause central nervous system (CNS) events, including: nervousness,
575 agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS** and **Information for**
576 **Patients.**)

577 Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest
578 as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering,
579 edema) involving areas exposed to light (typically the face, “V” area of the neck, extensor
580 surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolone
581 antibiotics after sun or UV light exposure. Therefore, excessive exposure to these sources of
582 light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (See
583 **ADVERSE REACTIONS** and **ADVERSE REACTIONS/ Post-Marketing Adverse**
584 **Event Reports**).

585 Prescribing AVELOX in the absence of a proven or strongly suspected bacterial infection or a
586 prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the

587 development of drug-resistant bacteria.

588 **Information for Patients:**

589 To assure safe and effective use of moxifloxacin, the following information and instructions
590 should be communicated to the patient when appropriate:

591 Patients should be advised:

- 592 • to contact their healthcare provider if they experience pain, swelling, or inflammation of a
593 tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and
594 discontinue AVELOX treatment. The risk of severe tendon disorder with fluoroquinolones is
595 higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs,
596 and in patients with kidney, heart or lung transplants.
- 597 • that antibacterial drugs including AVELOX should only be used to treat bacterial infections.
598 They do not treat viral infections (e.g., the common cold). When AVELOX is prescribed to
599 treat a bacterial infection, patients should be told that although it is common to feel better early
600 in the course of therapy, the medication should be taken exactly as directed. Skipping doses or
601 not completing the full course of therapy may (1) decrease the effectiveness of the immediate
602 treatment and (2) increase the likelihood that bacteria will develop resistance and will not be
603 treatable by AVELOX or other antibacterial drugs in the future.
- 604 • that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- 605 • that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine,
606 procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- 607 • that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride,
608 erythromycin, antipsychotics, and tricyclic antidepressants.
- 609 • to inform their physician of any personal or family history of QTc prolongation or
610 proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute
611 myocardial ischemia.
- 612 • to inform their physician of any other medications when taken concurrently with
613 moxifloxacin, including over-the-counter medications.
- 614 • to contact their physician if they experience palpitations or fainting spells while taking
615 moxifloxacin.
- 616 • that moxifloxacin tablets may be taken with or without meals, and to drink fluids liberally.
- 617 • that moxifloxacin tablets should be taken at least 4 hours before or 8 hours after multivitamins
618 (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate, or
619 VIDEX[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral solution.
620 (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug**
621 **Interactions.**)
- 622 • that moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic
623 reactions, even following a single dose, and to discontinue the drug at the first sign of a skin
624 rash or other signs of an allergic reaction.
- 625 • that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know
626 how they react to this drug before they operate an automobile or machinery or engage in
627 activities requiring mental alertness or coordination.
- 628 • that photosensitivity/phototoxicity has been reported in patients receiving quinolones.
629 Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or
630 UVA/B treatment) while taking quinolones. If patients need to be outdoors while using
631 quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and

632 discuss other sun protection measures with their physician. If a sunburn-like reaction or skin
633 eruption occurs, patients should contact their physician (see **CLINICAL**
634 **PHARMACOLOGY/ Photosensitivity Potential**).

- 635 • that convulsions have been reported in patients receiving quinolones, and they should notify
636 their physician before taking this drug if there is a history of this condition.
- 637 • that diarrhea is a common problem caused by antibiotics which usually ends when the
638 antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can
639 develop watery and bloody stools (with or without stomach cramps and fever) even as late as
640 two or more months after having taken the last dose of the antibiotic. If this occurs, patients
641 should contact their physician as soon as possible.

642 **Drug Interactions:**

643 Antacids, Sucralfate, Metal Cations, Multivitamins: Quinolones form chelates with alkaline
644 earth and transition metal cations. Oral administration of quinolones with antacids containing
645 aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins
646 containing iron or zinc, or with formulations containing divalent and trivalent cations such as
647 VIDEX[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may
648 substantially interfere with the absorption of quinolones, resulting in systemic concentrations
649 considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before
650 or 8 hours after these agents. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and
651 **DOSAGE AND ADMINISTRATION**.)

652 No clinically significant drug-drug interactions between itraconazole, theophylline, warfarin,
653 digoxin, atenolol, oral contraceptives or glyburide have been observed with moxifloxacin.
654 Itraconazole, theophylline, digoxin, probenecid, morphine, ranitidine, and calcium have been
655 shown not to significantly alter the pharmacokinetics of moxifloxacin. (See **CLINICAL**
656 **PHARMACOLOGY**.)

657 Warfarin: No significant effect of moxifloxacin on R- and S-warfarin was detected in a clinical
658 study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in
659 the presence of moxifloxacin. Quinolones, including moxifloxacin, have been reported to
660 enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In
661 addition, infectious disease and its accompanying inflammatory process, age, and general status
662 of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time,
663 International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely
664 monitored if a quinolone is administered concomitantly with warfarin or its derivatives.

665 Drugs metabolized by Cytochrome P450 enzymes: *In vitro* studies with cytochrome P450
666 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9,
667 CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of
668 drugs metabolized by these enzymes (e.g. midazolam, cyclosporine, warfarin, theophylline).

669 Nonsteroidal anti-inflammatory drugs (NSAIDs): Although not observed with moxifloxacin in
670 preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory
671 drug with a quinolone may increase the risks of CNS stimulation and convulsions. (See
672 **WARNINGS**.)

673 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

674 Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not
675 been performed.

676 Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in
677 the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed
678 with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA
679 gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation
680 assay. An equivocal result was obtained in the same assay when v79 cells were used.
681 Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce
682 unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity
683 *in vivo* in a micronucleus test or a dominant lethal test in mice.
684 Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500
685 mg/kg/day, approximately 12 times the maximum recommended human dose based on body
686 surface area (mg/m^2), or at intravenous doses as high as 45 mg/kg/day, approximately equal to
687 the maximum recommended human dose based on body surface area (mg/m^2). At 500 mg/kg
688 orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the
689 estrous cycle in female rats.

690 **Pregnancy: Teratogenic Effects. Pregnancy Category C:**

691 Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral
692 doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose based on
693 systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal skeletal
694 development (indicative of fetotoxicity) were observed. Intravenous administration of 80
695 mg/kg/day (approximately 2 times the maximum recommended human dose based on body
696 surface area (mg/m²)) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal
697 and placental weights and the appearance of the placenta. There was no evidence of teratogenicity
698 at intravenous doses as high as 80 mg/kg/day. Intravenous administration of 20 mg/kg/day
699 (approximately equal to the maximum recommended human oral dose based upon systemic
700 exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body weights and
701 delayed fetal skeletal ossification. When rib and vertebral malformations were combined, there
702 was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at
703 this dose included mortality, abortions, marked reduction of food consumption, decreased water
704 intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when
705 pregnant cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the
706 maximum recommended human dose based upon systemic exposure). An increased incidence of
707 smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study
708 conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of
709 pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival.
710 Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.
711 Since there are no adequate or well-controlled studies in pregnant women, moxifloxacin should
712 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

713 **Nursing Mothers:**

714 Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin may also be excreted in human
715 milk. Because of the potential for serious adverse reactions in infants who are nursing from
716 mothers taking moxifloxacin, a decision should be made whether to discontinue nursing or to
717 discontinue the drug, taking into account the importance of the drug to the mother.

718 **Pediatric Use:**

719 Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not
720 been established. Moxifloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

721 **Geriatric Use:**

722 Geriatric patients are at increased risk for developing severe tendon disorders including tendon
723 rupture when being treated with a fluoroquinolone such as AVELOX. This risk is further
724 increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon
725 rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or
726 after completion of therapy; cases occurring up to several months after fluoroquinolone
727 treatment have been reported. Caution should be used when prescribing AVELOX to elderly
728 patients especially those on corticosteroids. Patients should be informed of this potential side
729 effect and advised to discontinue AVELOX and contact their healthcare provider if any
730 symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and
731 **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

732 In controlled multiple-dose clinical trials, 23% of patients receiving oral moxifloxacin were
733 greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The
734 clinical trial data demonstrate that there is no difference in the safety and efficacy of oral

735 moxifloxacin in patients aged 65 or older compared to younger adults.
736 In trials of intravenous use, 42% of moxifloxacin patients were greater than or equal to 65 years
737 of age, and 23% were greater than or equal to 75 years of age. The clinical trial data demonstrate
738 that the safety of intravenous moxifloxacin in patients aged 65 or older was similar to that of
739 comparator-treated patients. In general, elderly patients may be more susceptible to drug-associated
740 effects of the QT interval. Therefore, AVELOX should be avoided in patients taking drugs that can
741 result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients
742 with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

743 **ADVERSE REACTIONS**

744 Clinical efficacy trials enrolled over 9,200 moxifloxacin orally and intravenously treated patients,
745 of whom over 8,600 patients received the 400 mg dose. Most adverse events reported in
746 moxifloxacin trials were described as mild to moderate in severity and required no treatment.
747 Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 2.9% of
748 orally treated patients and 6.3 % of sequentially (intravenous followed by oral) treated patients.
749 The latter studies were conducted in community acquired pneumonia and complicated skin and
750 skin structure infections and complicated intra-abdominal infections with, in general, a sicker
751 patient population compared to the tablet studies.

752 Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than
753 or equal to 2% of moxifloxacin treated patients were: nausea (6%), diarrhea (5%), dizziness (2%).

754 Additional clinically relevant uncommon events, judged by investigators to be at least possibly
755 drug-related, that occurred in greater than or equal to 0.1% and less than 2% of moxifloxacin
756 treated patients were:

757 **BODY AS A WHOLE:** abdominal pain, headache, asthenia, injection site reaction (including
758 phlebitis), malaise, moniliasis, pain, allergic reaction

759 **CARDIOVASCULAR:** tachycardia, palpitation, vasodilation, QT interval prolonged

760 **DIGESTIVE:** vomiting, abnormal liver function test, dyspepsia, dry mouth, flatulence, oral
761 moniliasis, constipation, GGTP increased, anorexia, stomatitis, glossitis

762 **HEMIC AND LYMPHATIC:** leukopenia, eosinophilia, prothrombin decrease (prothrombin time
763 prolonged/International Normalized Ratio (INR) increased), thrombocythemia

764 **METABOLIC AND NUTRITIONAL:** lactic dehydrogenase increased, amylase increased

765 **MUSCULOSKELETAL:** arthralgia, myalgia

766 **NERVOUS SYSTEM:** insomnia, nervousness, vertigo, somnolence, anxiety, tremor

767 **SKIN/APPENDAGES:** rash (maculopapular, purpuric, pustular), pruritus, sweating, urticaria

768 **SPECIAL SENSES:** taste perversion

769 **UROGENITAL:** vaginal moniliasis, vaginitis

770 Additional clinically relevant rare events, judged by investigators to be at least possibly
771 drug-related, that occurred in less than 0.1% of moxifloxacin treated patients were:

772 abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis,
773 asthma, atrial fibrillation, back pain, chest pain, confusion, convulsions, depersonalization,
774 depression, dysphagia, dyspnea, ECG abnormal, emotional lability, face edema, gastritis,
775 gastrointestinal disorder, hallucinations, hyperglycemia, hyperlipidemia, hypertension, hypertonia,
776 hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic),
777 kidney function abnormal, lab test abnormal (not specified), leg pain, paraesthesia, parosmia,
778 pelvic pain, peripheral edema, photosensitivity/phototoxicity reactions, pseudomembranous
779 colitis, prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR)
780 decreased), sleep disorders, speech disorders, supraventricular tachycardia, syncope, taste loss,

781 tendon disorder, thinking abnormal, thrombocytopenia, thromboplastin decrease, tinnitus, tongue
782 discoloration, ventricular tachycardia

783 **Post-Marketing Adverse Event Reports:**

784 Additional adverse events have been reported from worldwide post-marketing experience with
785 moxifloxacin. Because these events are reported voluntarily from a population of uncertain size, it
786 is not always possible to reliably estimate their frequency or establish a causal relationship to drug
787 exposure. These events, some of them life-threatening, include anaphylactic reaction,
788 anaphylactic shock, angioedema (including laryngeal edema), hepatic failure, including fatal
789 cases, hepatitis (predominantly cholestatic), photosensitivity/phototoxicity reaction (see
790 **PRECAUTIONS**), psychotic reaction, Stevens-Johnson syndrome, tendon rupture, toxic
791 epidermal necrolysis, and ventricular tachyarrhythmias (including in very rare cases cardiac
792 arrest and torsade de pointes, and usually in patients with concurrent severe underlying
793 proarrhythmic conditions).

794 **LABORATORY CHANGES**

795 Changes in laboratory parameters, without regard to drug relationship, which are not listed above
796 and which occurred in $\geq 2\%$ of patients and at an incidence greater than in controls included:
797 increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin,
798 bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose,
799 pO_2 , bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities
800 were caused by the drug or the underlying condition being treated.

801 **OVERDOSAGE**

802 Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the
803 event of acute overdose, the stomach should be emptied and adequate hydration maintained.
804 ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient
805 should be carefully observed and given supportive treatment. The administration of activated
806 charcoal as soon as possible after oral overdose may prevent excessive increase of systemic
807 moxifloxacin exposure. About 3% and 9% of the dose of moxifloxacin, as well as about 2% and
808 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and
809 hemodialysis, respectively.

810 Single oral moxifloxacin doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and
811 cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was
812 100 mg/kg. Toxic signs after administration of a single high dose of moxifloxacin to these
813 animals included CNS and gastrointestinal effects such as decreased activity, somnolence,
814 tremor, convulsions, vomiting and diarrhea.

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DOSAGE AND ADMINISTRATION

The dose of AVELOX is 400 mg (orally or as an intravenous infusion) once every 24 hours. The duration of therapy depends on the type of infection as described below.

Infection *	Daily Dose	Duration
Acute Bacterial Sinusitis	400 mg	10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5 days
Community Acquired Pneumonia	400 mg	7-14 days
Uncomplicated Skin and Skin Structure Infections	400 mg	7 days
Complicated Skin and Skin Structure Infections	400 mg	7 – 21 days
Complicated Intra-Abdominal Infections	400 mg	5-14 days

* due to the designated pathogens (See **INDICATIONS AND USAGE**). For I.V. use see **Precautions, Geriatric Use**.

For Complicated Intra-Abdominal Infections, therapy should usually be initiated with the intravenous formulation.

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

Oral doses of moxifloxacin should be administered at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug Interactions**.)

Impaired Renal Function

No dosage adjustment is required in renally impaired patients, including those on either hemodialysis or continuous ambulatory peritoneal dialysis.

Impaired Hepatic Function

No dosage adjustment is required in patients with mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in patients with severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See **CLINICAL PHARMACOLOGY, Hepatic Insufficiency**.)

AVELOX I.V. should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

AVELOX I.V. 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 I.V. or infused simultaneously through the same intravenous line. If the same

858 intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the
859 “piggyback” method of administration is used, the line should be flushed before and after
860 infusion of AVELOX I.V. with an infusion solution compatible with AVELOX I.V. as well as
861 with other drug(s) administered via this common line.

862 AVELOX I.V. is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:
863 0.9% Sodium Chloride Injection, USP Sterile Water for Injection, USP
864 1M Sodium Chloride Injection 10% Dextrose for Injection, USP
865 5% Dextrose Injection, USP Lactated Ringer’s for Injection

866 Preparation for administration of AVELOX I.V. injection premix in flexible containers:

- 867 1. Close flow control clamp of administration set.
- 868 2. Remove cover from port at bottom of container.
- 869 3. Insert piercing pin from an appropriate transfer set (e.g. one that does not require excessive force,
870 such as ISO compatible administration set) into port with a gentle twisting motion until pin is
871 firmly seated.

872 **NOTE:** Refer to complete directions that have been provided with the administration set.

873 **HOW SUPPLIED**

874 **Tablets**

875 AVELOX (moxifloxacin hydrochloride) Tablets are available as oblong, dull red film-coated
876 tablets containing 400 mg moxifloxacin.

877 The tablet is coded with the word “BAYER” on one side and “M400” on the reverse side.

878 Package	878 NDC Code
879 Bottles of 30:	0085-1733-01
880 Unit Dose Pack of 50:	0085-1733-02
881 ABC Pack of 5:	0085-1733-03

882 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room
883 Temperature]. Avoid high humidity.

884 **Intravenous Solution – Premix Bags**

885 AVELOX I.V. (moxifloxacin hydrochloride in sodium chloride injection) is available in
886 ready-to-use 250 mL latex-free flexible bags containing 400 mg of moxifloxacin in 0.8% saline.
887 **NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.**

888 Package	888 NDC Code
889 250 mL flexible container	0085-1737-01

890 Parenteral drug products should be inspected visually for particulate matter prior to administration.
891 Samples containing visible particulates should not be used.

892 Since the premix flexible containers are for single-use only, any unused portion should be discarded.
893 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room
894 Temperature].

895 **DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION.**

896 **ANIMAL PHARMACOLOGY**

897 Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile
898 dogs oral doses of moxifloxacin \geq 30 mg/kg/day (approximately 1.5 times the maximum
899 recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy.
900 There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and
901 500 mg/kg/day, respectively.

902 Unlike some other members of the quinolone class, crystalluria was not observed in 6 month
903 repeat dose studies in rats and monkeys with moxifloxacin.
904 No ocular toxicity was observed in a 13 week oral repeat dose study in dogs with a moxifloxacin
905 dose of 60 mg/kg/day. Ocular toxicity was not observed in 6 month repeat dose studies in rats and
906 monkeys (daily oral doses up to 500 mg/kg and 135 mg/kg, respectively). In beagle dogs,
907 electroretinographic (ERG) changes were observed in a 2 week study at oral doses of 60 and 90
908 mg/kg/day. Histopathological changes were observed in the retina from one of four dogs at 90
909 mg/kg/day, a dose associated with mortality in this study.
910 Some quinolones have been reported to have proconvulsant activity that is exacerbated with
911 concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs). Moxifloxacin at an oral dose
912 of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (e.g., seizures)
913 in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen.
914 In dog studies, at plasma concentrations about five times the human therapeutic level, a
915 QT-prolonging effect of moxifloxacin was found. Electrophysiological *in vitro* studies
916 suggested an inhibition of the rapid activating component of the delayed rectifier potassium
917 current (I_{Kr}) as an underlying mechanism. In dogs, the combined infusion of sotalol, a Class III
918 antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation than that
919 induced by the same dose (30 mg/kg) of moxifloxacin alone.
920 In a local tolerability study performed in dogs, no signs of local intolerance were seen when
921 moxifloxacin was administered intravenously. After intra-arterial injection, inflammatory
922 changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial
923 administration of moxifloxacin should be avoided.

924 CLINICAL STUDIES

925 Acute Bacterial Exacerbation of Chronic Bronchitis

926 AVELOX Tablets (400 mg once daily for five days) were evaluated for the treatment of acute
927 bacterial exacerbation of chronic bronchitis in a large, randomized, double-blind, controlled
928 clinical trial conducted in the US. This study compared AVELOX with clarithromycin (500 mg
929 twice daily for 10 days) and enrolled 629 patients. The primary endpoint for this trial was clinical
930 success at 7-17 days post-therapy. The clinical success for AVELOX was 89% (222/250)
931 compared to 89% (224/251) for clarithromycin.
932 The following outcomes are the clinical success rates at the follow-up visit for the clinically
933 evaluable patient groups by pathogen:

934 PATHOGEN	935 AVELOX	936 Clarithromycin
935 <i>Streptococcus pneumoniae</i>	16/16 (100%)	20/23 (87%)
936 <i>Haemophilus influenzae</i>	33/37 (89%)	36/41 (88%)
937 <i>Haemophilus parainfluenzae</i>	16/16 (100%)	14/14 (100%)
938 <i>Moraxella catarrhalis</i>	29/34 (85%)	24/24 (100%)
939 <i>Staphylococcus aureus</i>	15/16 (94%)	6/8 (75%)
940 <i>Klebsiella pneumoniae</i>	18/20 (90%)	10/11 (91%)

941 The microbiological eradication rates (eradication plus presumed eradication) in AVELOX
942 treated patients were *Streptococcus pneumoniae* 100%, *Haemophilus influenzae* 89%,
943 *Haemophilus parainfluenzae* 100%, *Moraxella catarrhalis* 85%, *Staphylococcus aureus* 94%,
944 and *Klebsiella pneumoniae* 85%.

945 **Community Acquired Pneumonia**

946 A large, randomized, double-blind, controlled clinical trial was conducted in the US to compare the
947 efficacy of AVELOX Tablets (400 mg once daily) to that of high-dose clarithromycin (500 mg twice
948 daily) in the treatment of patients with clinically and radiologically documented community acquired
949 pneumonia. This study enrolled 474 patients (382 of whom were valid for the primary efficacy
950 analysis conducted at the 14 - 35 day follow-up visit). Clinical success for clinically evaluable
951 patients was 95% (184/194) for AVELOX and 95% (178/188) for high dose clarithromycin.

952 A large, randomized, double-blind, controlled trial was conducted in the US and Canada to
953 compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days to an IV/PO
954 fluoroquinolone control (trovafloxacin or levofloxacin) in the treatment of patients with
955 clinically and radiologically documented community acquired pneumonia. This study enrolled
956 516 patients, 362 of whom were valid for the primary efficacy analysis conducted at the 7-30 day
957 post-therapy visit. The clinical success rate was 86% (157/182) for AVELOX therapy and 89%
958 (161/180) for the fluoroquinolone comparators.

959 An open-label ex-US study that enrolled 628 patients compared AVELOX to sequential IV/PO
960 amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO
961 clarithromycin (500 mg BID). The intravenous formulations of the comparators are not FDA
962 approved. The clinical success rate at Day 5-7 (the primary efficacy timepoint) for AVELOX
963 therapy was 93% (241/258) and demonstrated superiority to amoxicillin/clavulanate ±
964 clarithromycin (85%, 239/280) [95% C.I. 2.9%, 13.2%]. The clinical success rate at the 21-28 days
965 post-therapy visit for AVELOX was 84% (216/258), which also demonstrated superiority to the
966 comparators (74%, 208/280) [95% C.I. 2.6%, 16.3%].

967 The clinical success rates by pathogen across four CAP studies are presented below:

968 **Clinical Success Rates By Pathogen (Pooled CAP Studies)**

969	PATHOGEN	AVELOX	
970	<i>Streptococcus pneumoniae</i>	80/85	(94%)
971	<i>Staphylococcus aureus</i>	17/20	(85%)
972	<i>Klebsiella pneumoniae</i>	11/12	(92%)
973	<i>Haemophilus influenzae</i>	56/61	(92%)
974	<i>Chlamydia pneumoniae</i>	119/128	(93%)
975	<i>Mycoplasma pneumoniae</i>	73/76	(96%)
976	<i>Moraxella catarrhalis</i>	11/12	(92%)

977 **Community Acquired Pneumonia caused by Multi-Drug Resistant**

978 ***Streptococcus pneumoniae* (MDRSP)***

979 Avelox was effective in the treatment of community acquired pneumonia (CAP) caused by
980 multi-drug resistant *Streptococcus pneumoniae* MDRSP* isolates. Of 37 microbiologically
981 evaluable patients with MDRSP isolates, 35 patients (95%) achieved clinical and
982 bacteriological success post-therapy. The clinical and bacteriological success rates based on the
983 number of patients treated are shown in the table below.

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

988 **Clinical and Bacteriological Success Rates for Moxifloxacin-Treated MDRSP**
989 **CAP Patients (Population: Valid for Efficacy):**

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N ^a	%	n/N ^b	%
Penicillin-resistant	21/21	100%*	21/21	100%*
2 nd generation cephalosporin-resistant	25/26	96%*	25/26	96%*
Macrolide-resistant **	22/23	96%	22/23	96%
Trimethoprim/sulfamethoxazole-resistant	28/30	93%	28/30	93%
Tetracycline-resistant	17/18	94%	17/18	94%

990 ^a n = number of patients successfully treated; N = number of patients with MDRSP (from a total
991 of 37 patients)

992 ^b n = number of patients successfully treated (presumed eradication or eradication); N = number
993 of patients with MDRSP (from a total of 37 patients)

994 * One patient had a respiratory isolate that was resistant to penicillin and cefuroxime but a
995 blood isolate that was intermediate to penicillin and cefuroxime. The patient is included in the
996 database based on the respiratory isolate.

997 **Azithromycin, clarithromycin, and erythromycin were the macrolide antimicrobials tested.

998 Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates
999 are summarized in the table below:

1000

<i>S. pneumoniae</i> with MDRSP	Clinical Success	Bacteriological Eradication Rate
Resistant to 2 antimicrobials	12/13 (92.3 %)	12/13 (92.3 %)
Resistant to 3 antimicrobials	10/11 (90.9 %)*	10/11 (90.9 %)*
Resistant to 4 antimicrobials	6/6 (100%)	6/6 (100%)
Resistant to 5 antimicrobials	7/7 (100%)*	7/7 (100%)*
Bacteremia with MDRSP	9/9 (100%)	9/9 (100%)

1001 * One patient had a respiratory isolate resistant to 5 antimicrobials and a blood isolate resistant
1002 to 3 antimicrobials. The patient was included in the category resistant to 5 antimicrobials.

1003 **Acute Bacterial Sinusitis**

1004 In a large, controlled double-blind study conducted in the US, AVELOX Tablets (400 mg once
1005 daily for ten days) were compared with cefuroxime axetil (250 mg twice daily for ten days) for
1006 the treatment of acute bacterial sinusitis. The trial included 457 patients valid for the primary
1007 efficacy determination. Clinical success (cure plus improvement) at the 7 to 21 day post-therapy
1008 test of cure visit was 90% for AVELOX and 89% for cefuroxime.

1009 An additional non-comparative study was conducted to gather bacteriological data and to
1010 evaluate microbiological eradication in adult patients treated with AVELOX 400 mg once daily
1011 for seven days. All patients (n = 336) underwent antral puncture in this study. Clinical success
1012 rates and eradication/ presumed eradication rates at the 21 to 37 day follow-up visit were 97%
1013 (29 out of 30) for *Streptococcus pneumoniae*, 83% (15 out of 18) for *Moraxella catarrhalis*, and
1014 80% (24 out of 30) for *Haemophilus influenzae*.

1015 **Uncomplicated Skin and Skin Structure Infections**

1016 A randomized, double-blind, controlled clinical trial conducted in the US compared the efficacy
 1017 of AVELOX 400 mg once daily for seven days with cephalexin HCl 500 mg three times daily for
 1018 seven days. The percentage of patients treated for uncomplicated abscesses was 30%, furuncles
 1019 8%, cellulitis 16%, impetigo 20%, and other skin infections 26%. Adjunctive procedures (incision
 1020 and drainage or debridement) were performed on 17% of the AVELOX treated patients and 14%
 1021 of the comparator treated patients. Clinical success rates in evaluable patients were 89% (108/122)
 1022 for AVELOX and 91% (110/121) for cephalexin HCl.

1023 **Complicated Skin and Skin Structure Infections**

1024 Two randomized, active controlled trials of cSSSI were performed. A double-blind trial was
 1025 conducted primarily in North America to compare the efficacy of sequential IV/PO AVELOX 400
 1026 mg QD for 7-14 days to an IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of
 1027 patients with cSSSI. This study enrolled 617 patients, 335 of which were valid for the primary
 1028 efficacy analysis. A second open-label International study compared AVELOX 400 mg QD for 7-21
 1029 days to sequential IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of patients
 1030 with cSSSI. This study enrolled 804 patients, 632 of which were valid for the primary efficacy
 1031 analysis. Surgical incision and drainage or debridement was performed on 55% of the moxifloxacin
 1032 treated and 53% of the comparator treated patients in these studies and formed an integral part of
 1033 therapy for this indication. Success rates varied with the type of diagnosis ranging from 61% in
 1034 patients with infected ulcers to 90% in patients with complicated erysipelas. These rates were similar
 1035 to those seen with comparator drugs. The overall success rates in the evaluable patients and the
 1036 clinical success by pathogen are shown below:

1037 **Overall Clinical Success Rates in Patients with Complicated Skin and Skin**
 1038 **Structure Infections**

Study	Moxifloxacin n/ N (%)	Comparator n/N (%)	95% Confidence Interval
North America	125/162 (77.2%)	141/173 (81.5%)	-14.4%, 2%
International	254/315 (80.6%)	268/317 (84.5%)	-9.4%, 2.2%

1039 **Clinical Success Rates by Pathogen in Patients with Complicated Skin and Skin**
 1040 **Structure Infections**

Pathogen	Moxifloxacin n/ N (%)	Comparator n/N (%)
<i>Staphylococcus aureus</i> (methicillin-susceptible strains) *	106/129 (82.2%)	120/137 (87.6%)
<i>Escherichia coli</i>	31/38 (81.6 %)	28/33 (84.8 %)
<i>Klebsiella pneumoniae</i>	11/12 (91.7 %)	7/10 (70%)
<i>Enterobacter cloacae</i>	9/11 (81.8%)	4/7 (57.1%)

1041 * methicillin susceptibility was only determined in the North American Study

1042 **Complicated Intra-Abdominal Infections**

1043 Two randomized, active controlled trials of cIAI were performed. A double-blind trial was
1044 conducted primarily in North America to compare the efficacy of sequential IV/PO AVELOX 400
1045 mg QD for 5-14 days to IV/ piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in
1046 the treatment of patients with cIAI, including peritonitis, abscesses, appendicitis with perforation,
1047 and bowel perforation. This study enrolled 681 patients, 379 of which were considered clinically
1048 evaluable. A second open-label international study compared AVELOX 400 mg QD for 5-14 days to
1049 IV ceftriaxone plus IV metronidazole followed by PO amoxicillin/clavulanic acid in the treatment of
1050 patients with cIAI. This study enrolled 595 patients, 511 of which were considered clinically
1051 evaluable. The clinically evaluable population consisted of subjects with a surgically confirmed
1052 complicated infection, at least 5 days of treatment and a 25-50 day follow-up assessment for patients
1053 at the Test of Cure visit. The overall clinical success rates in the clinically evaluable patients are
1054 shown below:

1055 **Clinical Success Rates in Patients with Complicated Intra-Abdominal Infections**

Study	Moxifloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
North America (overall)	146/183 (79.8 %)	153/196 (78.1 %)	-7.4%,9.3%
Abscess	40/57 (70.2 %)	49/63 (77.8 %) *	NA ^a
Non-abscess	106/126 (84.1 %)	104/133 (78.2 %)	NA
International (overall)	199/246 (80.9 %)	218/265 (82.3 %)	-8.9 %,4.2%
Abscess	73/93 (78.5 %)	86/99 (86.9 %)	NA
Non-abscess	126/153 (82.4 %)	132/166 (79.5 %)	NA

1056 * excludes 2 patients who required additional surgery within the first 48 hours.

1057 ^aNA - not applicable

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1067 Manufactured by:



**Bayer HealthCare
Pharmaceuticals**

1068

1069 Bayer HealthCare Pharmaceuticals Inc.
1070 Wayne, NJ 07470

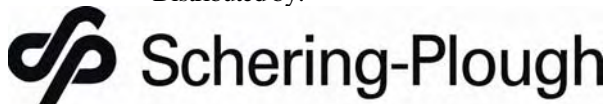
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Avelox Tablets made in Germany

1073 Avelox I.V. made in Germany
1074 or
1075 Avelox I.V. made in Norway by
1076 Fresenius Kabi Norge AS
1077 NO-1753 Halden, Norway

1078 Distributed by:



1079 Schering Corporation
1080 Kenilworth, NJ 07033
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MEDICATION GUIDE

AVELOX[®] (AV-eh-locks) **(moxifloxacin hydrochloride)** **Tablets**

AVELOX[®] I.V. (AV-eh-locks) **(moxifloxacin hydrochloride in sodium chloride injection)**

Read the Medication Guide that comes with AVELOX[®] before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about AVELOX?

AVELOX belongs to a class of antibiotics called fluoroquinolones. AVELOX can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take AVELOX.

- **Tendon rupture or swelling of the tendon (tendinitis)**
 - Tendons are tough cords of tissue that connect muscles to bones.
 - Pain, swelling, tears and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites can happen in people of all ages who take fluoroquinolone antibiotics, including AVELOX. The risk of getting tendon problems is higher if you:
 - are over 60 years of age
 - are taking steroids (corticosteroids)
 - have had a kidney, heart, or lung transplant
 - Swelling of the tendon (tendinitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors.
 - Other reasons for tendon ruptures can include:
 - physical activity or exercise
 - kidney failure
 - tendon problems in the past, such as in people with rheumatoid arthritis (RA)
 - Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking AVELOX until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is in the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of tendon rupture with continued use of AVELOX. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
 - Tendon rupture can happen while you are taking or after you have finished taking AVELOX. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.

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- Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
 - hear or feel a snap or pop in a tendon area
 - bruising right after an injury in a tendon area
 - unable to move the affected area or bear weight
- See the section “**What are the possible side effects of AVELOX?**” for more information about side effects.

What is AVELOX?

AVELOX is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by certain germs called bacteria in adults 18 years or older. It is not known if AVELOX is safe and works in people under 18 years of age. Children have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems while taking fluoroquinolone antibiotic medicines.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including AVELOX, do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking AVELOX.

Who should not take AVELOX?

Do not take AVELOX if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or if you are allergic to any of the ingredients in AVELOX. Ask your healthcare provider if you are not sure. See the list of ingredients in AVELOX at the end of this Medication Guide.

What should I tell my healthcare provider before taking AVELOX?

See “**What is the most important information I should know about AVELOX?**”

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation”
- have low blood potassium (hypokalemia)
- have a slow heart beat (bradycardia)
- have a history of seizures
- have kidney problems
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if AVELOX will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if AVELOX passes into breast milk. You and your healthcare provider should decide whether you will take AVELOX or breast-feed.

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Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal and dietary supplements. AVELOX and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take AVELOX or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See “**What are the possible side effects of AVELOX?**”.
- a blood thinner (warfarin, Coumadin, Jantoven)
- a medicine to control your heart rate or rhythm (antiarrhythmics). See “**What are the possible side effects of AVELOX?**”
- an anti-psychotic medicine
- a tricyclic antidepressant
- erythromycin
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See “**What is the most important information I should know about AVELOX?**”
- Certain medicines may keep AVELOX from working correctly. Take AVELOX either 4 hours before or 8 hours after taking these products:
 - an antacid or multivitamin, or other product that has magnesium, aluminum, iron, or zinc
 - sucralfate (Carafate)
 - didanosine (Videx®, Videx® EC)

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take AVELOX?

- Take AVELOX once a day exactly as prescribed by your healthcare provider.
- Take AVELOX at about the same time each day.
- AVELOX Tablets should be swallowed.
- AVELOX can be taken with or without food.
- Drink plenty of fluids while taking AVELOX.
- AVELOX I.V. is given to you by intravenous (I.V.) infusion into your vein slowly, over 60 minutes, as prescribed by your healthcare provider.
- Do not skip any doses, or stop taking AVELOX even if you begin to feel better, until you finish your prescribed treatment, unless:
 - you have tendon effects (see “**What is the most important information I should know about AVELOX?**”),
 - you have a serious allergic reaction (see “**What are the possible side effects of AVELOX?**”), or
 - your healthcare provider tells you to stop.
- This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to AVELOX. If this happens, AVELOX and other antibiotic medicines may not work in the future.

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- If you miss a dose of AVELOX, take it as soon as you remember. Do not take more than 1 dose of AVELOX in one day.
- If you take too much, call your healthcare provider or get medical help immediately.

What should I avoid while taking AVELOX?

- AVELOX can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how AVELOX affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. AVELOX can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking AVELOX, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of AVELOX?

AVELOX can cause side effects that may be serious or even cause death. See “**What is the most important information I should know about AVELOX?**”

Other serious side effects of AVELOX include:

- **Central Nervous System Effects**

Seizures have been reported in people who take fluoroquinolone antibiotics including AVELOX. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking AVELOX will change your risk of having a seizure. Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of AVELOX. Talk to your healthcare provider right away if you have any of these side effects, or other changes in mood or behavior:

- feeling dizzy
- seizures
- hear voices, see things, or sense things that are not there (hallucinations)
- feel restless
- tremors
- feel anxious or nervous
- confusion
- depression
- trouble sleeping
- feel more suspicious (paranoia)
- suicidal thought or acts
- nightmares

- **Serious allergic reactions**

Allergic reactions can happen in people taking fluoroquinolones, including AVELOX, even after only one dose. Stop taking AVELOX and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat

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- faint
- yellowing of the skin or eyes. Stop taking AVELOX and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to AVELOX (a liver problem).
- **Skin rash.** Skin rash may happen in people taking AVELOX, even after only one dose. Stop taking AVELOX at the first sign of a skin rash and call your healthcare provider. Skin rash may be sign of a more serious reaction to AVELOX.
- **Serious heart rhythm changes** (QT prolongation and torsade de pointes)
Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. Avelox may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:
 - who are elderly
 - with a family history of prolonged QT interval,
 - with low blood potassium (hypokalemia),
 - who take certain medicines to control heart rhythm (antiarrhythmics)
- **Intestine infection (Pseudomembranous colitis)**
Pseudomembranous colitis can happen with most antibiotics, including AVELOX. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage (Peripheral Neuropathy)**
Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including AVELOX. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
 - pain
 - burning
 - tingling
 - numbness
 - weaknessAVELOX may need to be stopped to prevent permanent nerve damage.
- **Sensitivity to sunlight (photosensitivity)**
See “**What should I avoid while taking AVELOX?**”

The most common side effects of AVELOX include nausea and diarrhea.

These are not all the possible side effects of AVELOX. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVELOX?
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- Store AVELOX 59–86°F (15–30°C)
- Keep AVELOX away from moisture (humidity)

Keep AVELOX and all medicines out of the reach of children.

General Information about AVELOX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AVELOX for a condition for which it is not prescribed. Do not give AVELOX to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about AVELOX. If you would like more information about AVELOX, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AVELOX that is written for healthcare professionals. For more information go to www.AVELOX.com or call 1-800-526-4099.

What are the ingredients in AVELOX?

- AVELOX Tablets:
 - Active ingredient: moxifloxacin hydrochloride
 - Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and ferric oxide.
- AVELOX I.V.:
 - Active ingredient: moxifloxacin hydrochloride
 - Inactive ingredients: sodium chloride, USP, water for injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

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Manufactured by:



**Bayer HealthCare
Pharmaceuticals**

Bayer HealthCare Pharmaceuticals Inc.
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