

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

5 08918409, R X

12/08

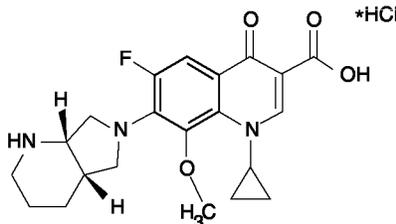
WARNING:

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

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

DESCRIPTION

9
 10 AVELOX (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is
 11 available as AVELOX Tablets for oral administration and as AVELOX I.V. for intravenous
 12 administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of
 13 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3
 14 quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular
 15 weight of 437.9. Its empirical formula is C₂₁H₂₄FN₃O₄ *HCl and its chemical structure is as
 16 follows:



17
 18 AVELOX Tablets are available as film-coated tablets containing moxifloxacin hydrochloride
 19 (equivalent to 400 mg moxifloxacin). The inactive ingredients are microcrystalline cellulose,
 20 lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium
 21 dioxide, polyethylene glycol and ferric oxide.

22 AVELOX I.V. is available in ready-to-use 250 mL latex-free flexibags as a sterile, preservative free,
 23 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg
 24 moxifloxacin) with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is
 25 yellow. The color does not affect, nor is it indicative of, product stability. The inactive
 26 ingredients are sodium chloride, USP, Water for Injection, USP, and may include hydrochloric
 27 acid and/or sodium hydroxide for pH adjustment. AVELOX I.V. contains approximately 34.2
 28 mEq (787 mg) of sodium in 250 mL.
 29

CLINICAL PHARMACOLOGY

31 **Absorption**

32 Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The
33 absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a
34 high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin.

35 Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate
36 of systemic absorption (AUC).

37 The mean (\pm SD) C_{\max} and AUC values following single and multiple doses of 400 mg
38 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	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	

39 * Range of means from different studies

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

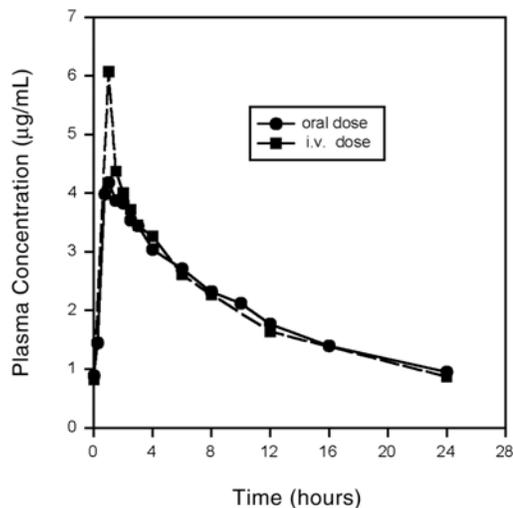
	C_{\max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose I.V. Healthy young male/female (n = 56)	3.9 \pm 0.9	39.3 \pm 8.6	8.2 - 15.4*
Patients (n = 118)			
Male (n = 64)	4.4 \pm 3.7		
Female (n = 54)	4.5 \pm 2		
< 65 years (n = 58)	4.6 \pm 4.2		
\geq 65 years (n = 60)	4.3 \pm 1.3		
Multiple Dose I.V. 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		

42 * Range of means from different studies

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

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

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



49

50 **Distribution**

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

60
61
62

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

Tissue or Fluid	N	Plasma Concentration ($\mu\text{g/mL}$)	Tissue or Fluid Concentration ($\mu\text{g/mL}$ or $\mu\text{g/g}$)	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	$3.7 \pm 1.1^{\dagger}$	7.6 ± 1.7	2 ± 0.3
Anterior Ethmoid Mucosa	3	$3.7 \pm 1.1^{\dagger}$	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	$3.7 \pm 1.1^{\dagger}$	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal				
Blister Fluid	5	$3 \pm 0.5^{\ddagger}$	2.6 ± 0.9	0.9 ± 0.2
Subcutaneous Tissue	6	$2.3 \pm 0.4^{\#}$	$0.9 \pm 0.3^*$	0.4 ± 0.6
Skeletal Muscle	6	$2.3 \pm 0.4^{\#}$	$0.9 \pm 0.2^*$	0.4 ± 0.1
Intra-Abdominal				
Abdominal tissue	8	2.9 ± 0.5	7.6 ± 2	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

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

66 [†] N = 5

67 [‡] N = 7

68 [#] N = 12

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

70 Metabolism

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

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

82 Excretion

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

87 Special Populations**88 Geriatric**

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

97 Pediatric

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

99 Gender

100 Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males
101 (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{\max} were 8% and 16%
102 higher, respectively, in females compared to males. There are no significant differences in
103 moxifloxacin pharmacokinetics between male and female subjects when differences in body
104 weight are taken into consideration.

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

108 Race

109 Steady-state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those
110 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
111 elimination half-life of 14 hours, following 400 mg p.o. daily.

112 Renal Insufficiency

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

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

125 The pharmacokinetics of single dose and multiple dose moxifloxacin were studied in patients with
126 $CL_{CR} < 20$ mL/min on either hemodialysis or continuous ambulatory peritoneal dialysis (8 HD, 8
127 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin in these HD and CAPD
128 patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of
129 moxifloxacin were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared
130 to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to
131 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of
132 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5 to 3,
133 compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin are not
134 microbiologically active, and the clinical implication of increased exposure to these metabolites in
135 patients with renal disease including those undergoing HD and CAPD has not been studied.
136 Oral administration of 400 mg QD moxifloxacin for 7 days to patients on HD or CAPD produced
137 mean systemic exposure (AUC_{ss}) to moxifloxacin similar to that generally seen in healthy
138 volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable
139 between CAPD patients and healthy volunteers. Both HD and CAPD removed only small
140 amounts of moxifloxacin from the body (approximately 9% by HD, and 3% by CAPD). HD and
141 CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

142 **Hepatic Insufficiency**

143 No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency
144 (Child-Pugh Classes A, B, or C). However, due to metabolic disturbances associated with hepatic
145 insufficiency, which may lead to QT prolongation, moxifloxacin should be used with caution in
146 these patients. (See WARNINGS and DOSAGE AND ADMINISTRATION).

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

151 The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging
152 up to 5.9-fold) and 5.7-fold (ranging up to 8-fold) in the mild and moderate groups,
153 respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (ranging
154 up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2)
155 increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased
156 by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of
157 increased exposure to the sulfate and glucuronide conjugates has not been studied. In a subset
158 of patients participating in a clinical trial, the plasma concentrations of moxifloxacin and
159 metabolites determined approximately at the moxifloxacin T_{max} following the first
160 intravenous or oral moxifloxacin dose in the Child-Pugh Class C patients (n=10) were similar
161 to those in the Child-Pugh Class A/B patients (n=5), and also similar to those observed in
162 healthy volunteer studies.

163 **Photosensitivity Potential**

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

170 **PRECAUTIONS, Information for Patients.)**

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

178 **Drug-drug Interactions**

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

188 As with all other quinolones, iron and antacids significantly reduced bioavailability of
189 moxifloxacin.

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

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

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

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

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

214 a single dose of moxifloxacin.

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

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

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

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

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

234 **Calcium:** Twelve healthy volunteers were administered concomitant moxifloxacin (single 400
235 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement) followed by an additional
236 two doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no
237 significant effect on the mean AUC of moxifloxacin. The mean C_{\max} was slightly reduced and the
238 time to maximum plasma concentration was prolonged when moxifloxacin was given with
239 calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours). These
240 differences are not considered to be clinically significant.

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

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

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

258 69) and 3 msec (\pm 29) on Day 3 (n = 290). (See **WARNINGS**.)
259 There is limited information available on the potential for a pharmacodynamic interaction in
260 humans between moxifloxacin and other drugs that prolong the QTc interval of the
261 electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the
262 QTc interval when combined with high doses of intravenous (I.V.) moxifloxacin in dogs.
263 Therefore, moxifloxacin should be avoided with Class IA and Class III antiarrhythmics. (See
264 **ANIMAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS**.)

265 **MICROBIOLOGY**

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

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

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

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

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

285 **Aerobic Gram-positive microorganisms**

286 *Enterococcus faecalis* (many strains are only moderately susceptible)

287 *Staphylococcus aureus* (methicillin-susceptible strains only)

288 *Streptococcus anginosus*

289 *Streptococcus constellatus*

290 *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]*)

291 *Streptococcus pyogenes*

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

296 **Aerobic Gram-negative microorganisms**297 *Enterobacter cloacae*298 *Escherichia coli*299 *Haemophilus influenzae*300 *Haemophilus parainfluenzae*301 *Klebsiella pneumoniae*302 *Moraxella catarrhalis*303 *Proteus mirabilis*304 **Anaerobic microorganisms**305 *Bacteroides fragilis*306 *Bacteroides thetaiotaomicron*307 *Clostridium perfringens*308 *Peptostreptococcus* species309 **Other microorganisms**310 *Chlamydia pneumoniae*311 *Mycoplasma pneumoniae*312 The following *in vitro* data are available, **but their clinical significance is unknown.**

313 Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 µg/mL or less
 314 against most (≥ 90%) strains of the following microorganisms; however, the safety and
 315 effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not
 316 been established in adequate and well-controlled clinical trials.

317 **Aerobic Gram-positive microorganisms**318 *Staphylococcus epidermidis* (methicillin-susceptible strains only)319 *Streptococcus agalactiae*320 *Streptococcus viridans* group321 **Aerobic Gram-negative microorganisms**322 *Citrobacter freundii*323 *Klebsiella oxytoca*324 *Legionella pneumophila*325 **Anaerobic microorganisms**326 *Fusobacterium* species327 *Prevotella* species328 **Susceptibility Tests**

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

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

	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
337	≤ 2	Susceptible (S)
338	4	Intermediate (I)
339	≥ 8	Resistant (R)

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

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1	Susceptible (S)

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

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

348 For testing *Streptococcus* species including *Streptococcus pneumoniae* ^b and *Enterococcus*
349 *faecalis*:

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

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

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

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

<u>Microorganism</u>		<u>MIC (µg/mL)</u>
<i>Enterococcus faecalis</i>	ATCC 29212	0.06 - 0.5
<i>Escherichia coli</i>	ATCC 25922	0.008 - 0.06
<i>Haemophilus influenzae</i>	ATCC 49247 ^c	0.008 - 0.03
<i>Staphylococcus aureus</i>	ATCC 29213	0.015 - 0.06
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^d	0.06 - 0.25

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

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

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

385 Reports from the laboratory providing results of the standard single-disk susceptibility test with a
 386 5- μ g moxifloxacin disk should be interpreted according to the following criteria:
 387 The following zone diameter interpretive criteria should be used for testing Enterobacteriaceae
 388 and methicillin-susceptible *Staphylococcus aureus*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
16 – 18	Intermediate (I)
≤ 15	Resistant (R)

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

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 18	Susceptible (S)

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

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

401 For testing *Streptococcus* species including *Streptococcus pneumoniae*^f and *Enterococcus*
 402 *faecalis*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 18	Susceptible (S)
15 – 17	Intermediate (I)
≤ 14	Resistant (R)

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

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

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

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

420 ^gThese quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using
 421 *Haemophilus* Test Medium (HTM)².

422 ^hThese quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC
 423 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5%
 424 sheep blood and incubated in 5% CO₂.

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

	<u>MIC (ug/mL)</u>	<u>Interpretation</u>
428	≤ 2	Susceptible (S)
429	4	Intermediate (I)
430	≥ 8	Resistant (R)

432 ⁱThis interpretive standard is applicable to reference agar dilution susceptibility tests using
 433 *Brucella* agar supplemented with hemin, vitamin K₁ and 5% laked sheep blood.

434 Acceptable ranges of MICs (ug/mL) for control strains for reference agar dilution testing ^j:

<u>Microorganism</u>		<u>MIC (ug/mL)</u>
<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

435 ^jThese quality control ranges are applicable to reference agar dilution tests using *Brucella* agar
 436 supplemented with hemin, vitamin K₁ and 5% laked sheep blood.

437 **INDICATIONS AND USAGE**

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

442 **Acute Bacterial Sinusitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or
 443 *Moraxella catarrhalis*.

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

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

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

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

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

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

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

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

474 **CONTRAINDICATIONS**

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

477 **WARNINGS**

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

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

498 **QT prolongation:** Moxifloxacin has been shown to prolong the QT interval of the
499 electrocardiogram in some patients. The drug should be avoided in patients with known
500 prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving
501 Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic
502 agents, due to the lack of clinical experience with the drug in these patient populations.
503 Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such
504 as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed.
505 An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be
506 exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials,
507 the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator

508 treated patients who received concomitant therapy with drugs known to prolong the QTc interval.
509 Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such
510 as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT
511 prolongation may increase with increasing concentrations of the drug or increasing rates of
512 infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should
513 not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias
514 including torsade de pointes. No cardiovascular morbidity or mortality attributable to QTc
515 prolongation occurred with moxifloxacin treatment in over 9,200 patients in controlled clinical
516 studies, including 223 patients who were hypokalemic at the start of treatment, and there was no
517 increase in mortality in over 18,000 moxifloxacin tablet treated patients in a post-marketing
518 observational study in which ECGs were not performed. (See **CLINICAL PHARMACOLOGY,**
519 **Electrocardiogram.** For I.V. use, see **DOSAGE AND ADMINISTRATION** and
520 **PRECAUTIONS, Geriatric Use.**) In addition, moxifloxacin should be used with caution in
521 patients with mild, moderate, or severe liver cirrhosis. (See **CLINICAL PHARMACOLOGY,**
522 **Hepatic Insufficiency**).

523 The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological
524 examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage.
525 Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other
526 signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY.**)
527 Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central
528 nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression,
529 and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these
530 reactions occur in patients receiving moxifloxacin, the drug should be discontinued and appropriate
531 measures instituted. As with all quinolones, moxifloxacin should be used with caution in patients
532 with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the
533 presence of other risk factors that may predispose to seizures or lower the seizure threshold. (See
534 **PRECAUTIONS: General, Information for Patients,** and **ADVERSE REACTIONS.**)

535 **Hypersensitivity reactions:** Serious anaphylactic reactions, some following the first dose,
536 have been reported in patients receiving quinolone therapy, including moxifloxacin. Some
537 reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling,
538 pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions
539 require immediate emergency treatment with epinephrine. Moxifloxacin should be discontinued
540 at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous
541 steroids, and airway management, including intubation, may be administered as indicated.

542 Other serious and sometimes fatal events, some due to hypersensitivity, and some due to
543 uncertain etiology, have been reported rarely in patients receiving therapy with quinolones,
544 including AVELOX. These events may be severe and generally occur following the
545 administration of multiple doses. Clinical manifestations may include one or more of the
546 following:

- 547 • fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis,
548 Stevens-Johnson syndrome);
- 549 • vasculitis; arthralgia; myalgia; serum sickness;
- 550 • allergic pneumonitis;
- 551 • interstitial nephritis; acute renal insufficiency or failure;
- 552 • hepatitis; jaundice; acute hepatic necrosis or failure;
- 553 • anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic

554 thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other
555 hematologic abnormalities.

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

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

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

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

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

576 **PRECAUTIONS**

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

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

588 Prescribing AVELOX in the absence of a proven or strongly suspected bacterial infection or a
589 prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the
590 development of drug-resistant bacteria.

591 **Information for Patients:**

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

594 Patients should be advised:

- 595 • to contact their healthcare provider if they experience pain, swelling, or inflammation of a
596 tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and
597 discontinue AVELOX treatment. The risk of severe tendon disorder with fluoroquinolones is
598 higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs,

- 599 and in patients with kidney, heart or lung transplants.
- 600 • that antibacterial drugs including AVELOX should only be used to treat bacterial infections.
- 601 They do not treat viral infections (e.g., the common cold). When AVELOX is prescribed to
- 602 treat a bacterial infection, patients should be told that although it is common to feel better early
- 603 in the course of therapy, the medication should be taken exactly as directed. Skipping doses or
- 604 not completing the full course of therapy may (1) decrease the effectiveness of the immediate
- 605 treatment and (2) increase the likelihood that bacteria will develop resistance and will not be
- 606 treatable by AVELOX or other antibacterial drugs in the future.
- 607 • that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- 608 • that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine,
- 609 procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- 610 • that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride,
- 611 erythromycin, antipsychotics, and tricyclic antidepressants.
- 612 • to inform their physician of any personal or family history of QTc prolongation or
- 613 proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute
- 614 myocardial ischemia.
- 615 • to inform their physician of any other medications when taken concurrently with
- 616 moxifloxacin, including over-the-counter medications.
- 617 • to contact their physician if they experience palpitations or fainting spells while taking
- 618 moxifloxacin.
- 619 • that moxifloxacin tablets may be taken with or without meals, and to drink fluids liberally.
- 620 • that moxifloxacin tablets should be taken at least 4 hours before or 8 hours after multivitamins
- 621 (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate, or
- 622 VIDEX[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral solution.
- 623 (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug**
- 624 **Interactions.**)
- 625 • that moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic
- 626 reactions, even following a single dose, and to discontinue the drug at the first sign of a skin
- 627 rash or other signs of an allergic reaction.
- 628 • that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know
- 629 how they react to this drug before they operate an automobile or machinery or engage in
- 630 activities requiring mental alertness or coordination.
- 631 • that photosensitivity/phototoxicity has been reported in patients receiving quinolones.
- 632 Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or
- 633 UVA/B treatment) while taking quinolones. If patients need to be outdoors while using
- 634 quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and
- 635 discuss other sun protection measures with their physician. If a sunburn-like reaction or skin
- 636 eruption occurs, patients should contact their physician (see **CLINICAL**
- 637 **PHARMACOLOGY/Photosensitivity Potential**).
- 638 • that convulsions have been reported in patients receiving quinolones, and they should notify
- 639 their physician before taking this drug if there is a history of this condition.
- 640 • that diarrhea is a common problem caused by antibiotics which usually ends when the
- 641 antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can
- 642 develop watery and bloody stools (with or without stomach cramps and fever) even as late as
- 643 two or more months after having taken the last dose of the antibiotic. If this occurs, patients

644 should contact their physician as soon as possible.

645 **Drug Interactions:**

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

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

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

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

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

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

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

679 Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in
680 the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed
681 with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA
682 gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation
683 assay. An equivocal result was obtained in the same assay when v79 cells were used.
684 Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce
685 unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity
686 *in vivo* in a micronucleus test or a dominant lethal test in mice.

687 Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500

688 mg/kg/day, approximately 12 times the maximum recommended human dose based on body
689 surface area (mg/m^2), or at intravenous doses as high as 45 mg/kg/day, approximately equal to
690 the maximum recommended human dose based on body surface area (mg/m^2). At 500 mg/kg
691 orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the
692 estrous cycle in female rats.

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

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

716 **Nursing Mothers:**

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

721 **Pediatric Use:**

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

724 **Geriatric Use:**

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

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

738 moxifloxacin in patients aged 65 or older compared to younger adults.
 739 In trials of intravenous use, 42% of moxifloxacin patients were greater than or equal to 65 years
 740 of age, and 23% were greater than or equal to 75 years of age. The clinical trial data demonstrate
 741 that the safety of intravenous moxifloxacin in patients aged 65 or older was similar to that of
 742 comparator-treated patients. In general, elderly patients may be more susceptible to drug-associated
 743 effects of the QT interval. Therefore, AVELOX should be avoided in patients taking drugs that can
 744 result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients
 745 with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).
 746

747 **ADVERSE REACTIONS**

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

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

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

761 **BODY AS A WHOLE:** abdominal pain, headache, asthenia, dehydration (secondary to
 762 diarrhea or reduced fluid intake), injection site reaction (including phlebitis), malaise,
 763 moniliasis, pain, allergic reaction

764 **CARDIOVASCULAR:** cardiac arrhythmia (not otherwise specified), tachycardia, palpitation,
 765 vasodilation, QT interval prolonged

766 **DIGESTIVE:** vomiting, abnormal liver function test, increased transaminases, increased
 767 bilirubin), dyspepsia, dry mouth, flatulence, oral moniliasis, constipation, GGTP increased,
 768 anorexia, stomatitis, glossitis

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

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

772 **MUSCULOSKELETAL:** arthralgia, myalgia

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

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

775 **SPECIAL SENSES:** taste perversion

776 **UROGENITAL:** vaginal moniliasis, vaginitis

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

779 abnormal dreams, abnormal vision, (visual disturbances temporally associated with CNS
 780 symptoms), agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation,
 781 back pain, chest pain, confusion, convulsions of various clinical manifestations (including grand
 782 mal convulsions), depersonalization, depression (potentially culminating in self-endangering

783 behavior), dysphagia, dyspnea, ECG abnormal, emotional lability, face edema, gastritis,
784 gastrointestinal disorder, hallucinations, hyperglycemia, hyperlipidemia, hypertension, hypertonia,
785 hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic),
786 kidney function abnormal, lab test abnormal (not specified), leg pain, paraesthesia, parosmia,
787 pelvic pain, peripheral edema, photosensitivity/phototoxicity reactions, pseudomembranous
788 colitis, prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR)
789 decreased), sleep disorders, speech disorders, supraventricular tachycardia, syncope, taste loss,
790 tendon disorder, thinking abnormal, thrombocytopenia, thromboplastin decrease, tinnitus, tongue
791 discoloration, ventricular tachycardia

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

793 Additional adverse events have been reported from worldwide post-marketing experience with
794 moxifloxacin. Because these events are reported voluntarily from a population of uncertain size, it
795 is not always possible to reliably estimate their frequency or establish a causal relationship to drug
796 exposure. These events, some of them life-threatening, include anaphylactic reaction,
797 anaphylactic shock, angioedema (including laryngeal edema), hepatic failure, including fatal
798 cases, hepatitis (predominantly cholestatic), photosensitivity/phototoxicity reaction (see
799 **PRECAUTIONS**), psychotic reaction (very rarely culminating in self-endangering behavior),
800 renal dysfunction or renal failure, Stevens-Johnson syndrome, tendon rupture, toxic epidermal
801 necrolysis, and ventricular tachyarrhythmias (including in very rare cases cardiac arrest and
802 torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic
803 conditions). Cases of altered coordination and abnormal gait have also been reported.

804 **LABORATORY CHANGES**

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

811 **OVERDOSAGE**

812 Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the
813 event of acute overdose, the stomach should be emptied and adequate hydration maintained.
814 ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient
815 should be carefully observed and given supportive treatment. The administration of activated
816 charcoal as soon as possible after oral overdose may prevent excessive increase of systemic
817 moxifloxacin exposure. About 3% and 9% of the dose of moxifloxacin, as well as about 2% and
818 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and
819 hemodialysis, respectively.

820 Single oral moxifloxacin doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and
821 cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was
822 100 mg/kg. Toxic signs after administration of a single high dose of moxifloxacin to these
823 animals included CNS and gastrointestinal effects such as decreased activity, somnolence,
824 tremor, convulsions, vomiting and diarrhea.

DOSAGE AND ADMINISTRATION

825
826 The dose of AVELOX is 400 mg (orally or as an intravenous infusion) once every 24 hours. The
827 duration of therapy depends on the type of infection as described below.

828	Infection *	Daily Dose	Duration
829	Acute Bacterial Sinusitis	400 mg	10 days
830	Acute Bacterial Exacerbation	400 mg	5 days
831	of Chronic Bronchitis		
832	Community Acquired Pneumonia	400 mg	7-14 days
833	Uncomplicated Skin and	400 mg	7 days
834	Skin Structure Infections		
835	Complicated Skin and	400 mg	7 – 21 days
836	Skin Structure Infections		
837	Complicated Intra-Abdominal	400 mg	5-14 days
838	Infections		
839			

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

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

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

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

852 **Impaired Renal Function**

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

855 **Impaired Hepatic Function**

856 No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency
857 (Child-Pugh Classes A, B, or C). (See **CLINICAL PHARMACOLOGY, Hepatic**
858 **Insufficiency.**)

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

861 AVELOX I.V. should be administered by intravenous infusion over a period of 60 minutes by
862 direct infusion or through a Y-type intravenous infusion set which may already be in place.
863 **CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.**

864 Since only limited data are available on the compatibility of moxifloxacin intravenous injection
865 with other intravenous substances, additives or other medications should not be added to
866 AVELOX I.V. or infused simultaneously through the same intravenous line. If the same
867 intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the

868 “piggyback” method of administration is used, the line should be flushed before and after
 869 infusion of AVELOX I.V. with an infusion solution compatible with AVELOX I.V. as well as
 870 with other drug(s) administered via this common line.

871 AVELOX I.V. is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

872 0.9% Sodium Chloride Injection, USP	Sterile Water for Injection, USP
873 1M Sodium Chloride Injection	10% Dextrose for Injection, USP
874 5% Dextrose Injection, USP	Lactated Ringer’s for Injection

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

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

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

882 HOW SUPPLIED

883 Tablets

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

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

887 Package	NDC Code
888 Bottles of 30:	0085-1733-01
889 Unit Dose Pack of 50:	0085-1733-02
890 ABC Pack of 5:	0085-1733-03

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

893 Intravenous Solution – Premix Bags

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

897 Package	NDC Code
898 250 mL flexible container	0085-1737-01

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

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

904 DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION.

905 ANIMAL PHARMACOLOGY

906 Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile
 907 dogs oral doses of moxifloxacin \geq 30 mg/kg/day (approximately 1.5 times the maximum
 908 recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy.
 909 There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and
 910 500 mg/kg/day, respectively.

911 Unlike some other members of the quinolone class, crystalluria was not observed in 6 month

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

933 **CLINICAL STUDIES**

934 **Acute Bacterial Exacerbation of Chronic Bronchitis**

935 AVELOX Tablets (400 mg once daily for five days) were evaluated for the treatment of acute
 936 bacterial exacerbation of chronic bronchitis in a large, randomized, double-blind, controlled
 937 clinical trial conducted in the US. This study compared AVELOX with clarithromycin (500 mg
 938 twice daily for 10 days) and enrolled 629 patients. The primary endpoint for this trial was clinical
 939 success at 7-17 days post-therapy. The clinical success for AVELOX was 89% (222/250)
 940 compared to 89% (224/251) for clarithromycin.

941 The following outcomes are the clinical success rates at the follow-up visit for the clinically
 942 evaluable patient groups by pathogen:

943 <u>PATHOGEN</u>	<u>AVELOX</u>		<u>Clarithromycin</u>	
944 <i>Streptococcus pneumoniae</i>	16/16	(100%)	20/23	(87%)
945 <i>Haemophilus influenzae</i>	33/37	(89%)	36/41	(88%)
946 <i>Haemophilus parainfluenzae</i>	16/16	(100%)	14/14	(100%)
947 <i>Moraxella catarrhalis</i>	29/34	(85%)	24/24	(100%)
948 <i>Staphylococcus aureus</i>	15/16	(94%)	6/8	(75%)
949 <i>Klebsiella pneumoniae</i>	18/20	(90%)	10/11	(91%)

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

954 **Community Acquired Pneumonia**

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

961 A large, randomized, double-blind, controlled trial was conducted in the US and Canada to
 962 compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days to an IV/PO
 963 fluoroquinolone control (trovafloxacin or levofloxacin) in the treatment of patients with
 964 clinically and radiologically documented community acquired pneumonia. This study enrolled
 965 516 patients, 362 of whom were valid for the primary efficacy analysis conducted at the 7-30 day
 966 post-therapy visit. The clinical success rate was 86% (157/182) for AVELOX therapy and 89%
 967 (161/180) for the fluoroquinolone comparators.

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

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

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

978	<u>PATHOGEN</u>	<u>AVELOX</u>
979	<i>Streptococcus pneumoniae</i>	80/85 (94%)
980	<i>Staphylococcus aureus</i>	17/20 (85%)
981	<i>Klebsiella pneumoniae</i>	11/12 (92%)
982	<i>Haemophilus influenzae</i>	56/61 (92%)
983	<i>Chlamydia pneumoniae</i>	119/128 (93%)
984	<i>Mycoplasma pneumoniae</i>	73/76 (96%)
985	<i>Moraxella catarrhalis</i>	11/12 (92%)

986 **Community Acquired Pneumonia caused by Multi-Drug Resistant**
 987 ***Streptococcus pneumoniae* (MDRSP)***

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

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

997 **Clinical and Bacteriological Success Rates for Moxifloxacin-Treated MDRSP**
 998 **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%

999 ^a n = number of patients successfully treated; N = number of patients with MDRSP (from a total
 1000 of 37 patients)

1001 ^b n = number of patients successfully treated (presumed eradication or eradication); N = number
 1002 of patients with MDRSP (from a total of 37 patients)

1003 * One patient had a respiratory isolate that was resistant to penicillin and cefuroxime but a
 1004 blood isolate that was intermediate to penicillin and cefuroxime. The patient is included in the
 1005 database based on the respiratory isolate.

1006 **Azithromycin, clarithromycin, and erythromycin were the macrolide antimicrobials tested.

1007 Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates
 1008 are summarized in the table below:

1009

<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%)

1010 * One patient had a respiratory isolate resistant to 5 antimicrobials and a blood isolate resistant
 1011 to 3 antimicrobials. The patient was included in the category resistant to 5 antimicrobials.

1012 **Acute Bacterial Sinusitis**

1013 In a large, controlled double-blind study conducted in the US, AVELOX Tablets (400 mg once
 1014 daily for ten days) were compared with cefuroxime axetil (250 mg twice daily for ten days) for
 1015 the treatment of acute bacterial sinusitis. The trial included 457 patients valid for the primary
 1016 efficacy determination. Clinical success (cure plus improvement) at the 7 to 21 day post-therapy
 1017 test of cure visit was 90% for AVELOX and 89% for cefuroxime.

1018 An additional non-comparative study was conducted to gather bacteriological data and to
 1019 evaluate microbiological eradication in adult patients treated with AVELOX 400 mg once daily
 1020 for seven days. All patients (n = 336) underwent antral puncture in this study. Clinical success
 1021 rates and eradication/ presumed eradication rates at the 21 to 37 day follow-up visit were 97%
 1022 (29 out of 30) for *Streptococcus pneumoniae*, 83% (15 out of 18) for *Moraxella catarrhalis*, and
 1023 80% (24 out of 30) for *Haemophilus influenzae*.

1024 **Uncomplicated Skin and Skin Structure Infections**

1025 A randomized, double-blind, controlled clinical trial conducted in the US compared the efficacy
 1026 of AVELOX 400 mg once daily for seven days with cephalexin HCl 500 mg three times daily for
 1027 seven days. The percentage of patients treated for uncomplicated abscesses was 30%, furuncles
 1028 8%, cellulitis 16%, impetigo 20%, and other skin infections 26%. Adjunctive procedures (incision
 1029 and drainage or debridement) were performed on 17% of the AVELOX treated patients and 14%
 1030 of the comparator treated patients. Clinical success rates in evaluable patients were 89% (108/122)
 1031 for AVELOX and 91% (110/121) for cephalexin HCl.

1032 **Complicated Skin and Skin Structure Infections**

1033 Two randomized, active controlled trials of cSSSI were performed. A double-blind trial was
 1034 conducted primarily in North America to compare the efficacy of sequential IV/PO AVELOX 400
 1035 mg QD for 7-14 days to an IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of
 1036 patients with cSSSI. This study enrolled 617 patients, 335 of which were valid for the primary
 1037 efficacy analysis. A second open-label International study compared AVELOX 400 mg QD for 7-21
 1038 days to sequential IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of patients
 1039 with cSSSI. This study enrolled 804 patients, 632 of which were valid for the primary efficacy
 1040 analysis. Surgical incision and drainage or debridement was performed on 55% of the moxifloxacin
 1041 treated and 53% of the comparator treated patients in these studies and formed an integral part of
 1042 therapy for this indication. Success rates varied with the type of diagnosis ranging from 61% in
 1043 patients with infected ulcers to 90% in patients with complicated erysipelas. These rates were similar
 1044 to those seen with comparator drugs. The overall success rates in the evaluable patients and the
 1045 clinical success by pathogen are shown below:

1046 **Overall Clinical Success Rates in Patients with Complicated Skin and Skin**
 1047 **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%

1048 **Clinical Success Rates by Pathogen in Patients with Complicated Skin and Skin**
 1049 **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%)

1050 * methicillin susceptibility was only determined in the North American Study

1051 **Complicated Intra-Abdominal Infections**

1052 Two randomized, active controlled trials of cIAI were performed. A double-blind trial was
 1053 conducted primarily in North America to compare the efficacy of sequential IV/PO AVELOX 400
 1054 mg QD for 5-14 days to IV/ piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in
 1055 the treatment of patients with cIAI, including peritonitis, abscesses, appendicitis with perforation,
 1056 and bowel perforation. This study enrolled 681 patients, 379 of which were considered clinically
 1057 evaluable. A second open-label international study compared AVELOX 400 mg QD for 5-14 days to
 1058 IV ceftriaxone plus IV metronidazole followed by PO amoxicillin/clavulanic acid in the treatment of
 1059 patients with cIAI. This study enrolled 595 patients, 511 of which were considered clinically
 1060 evaluable. The clinically evaluable population consisted of subjects with a surgically confirmed
 1061 complicated infection, at least 5 days of treatment and a 25-50 day follow-up assessment for patients
 1062 at the Test of Cure visit. The overall clinical success rates in the clinically evaluable patients are
 1063 shown below:

1064 **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

1065 * excludes 2 patients who required additional surgery within the first 48 hours.

1066 ^aNA - not applicable

1067 **REFERENCES:** 1. Clinical and Laboratory Standards Institute, Methods for Dilution
 1068 Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Sixth Edition. Approved
 1069 Standard CLSI Document M7-A6, Vol. 23, No. 2, CLSI, Wayne, PA, January, 2003.
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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.

- 1116 • Get medical help right away if you get any of the following signs or symptoms of a
 1117 tendon rupture:
- 1118 • hear or feel a snap or pop in a tendon area
 - 1119 • bruising right after an injury in a tendon area
 - 1120 • unable to move the affected area or bear weight
- 1121 • See the section “**What are the possible side effects of AVELOX?**” for more
 1122 information about side effects.

1123 **What is AVELOX?**

1124 AVELOX is a fluoroquinolone antibiotic medicine used to treat certain types of infections
 1125 caused by certain germs called bacteria in adults 18 years or older. It is not known if AVELOX is
 1126 safe and works in people under 18 years of age. Children have a higher chance of getting bone,
 1127 joint, and tendon (musculoskeletal) problems while taking fluoroquinolone antibiotic medicines.

1128 Sometimes infections are caused by viruses rather than by bacteria. Examples include viral
 1129 infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including
 1130 AVELOX, do not kill viruses.

1131 Call your healthcare provider if you think your condition is not getting better while you are
 1132 taking AVELOX.

1133 **Who should not take AVELOX?**

1134 Do not take AVELOX if you have ever had a severe allergic reaction to an antibiotic known as
 1135 a fluoroquinolone, or if you are allergic to any of the ingredients in AVELOX. Ask your
 1136 healthcare provider if you are not sure. See the list of ingredients in AVELOX at the end of this
 1137 Medication Guide.

1138 **What should I tell my healthcare provider before taking 1139 AVELOX?**

1140 See “**What is the most important information I should know about AVELOX?**”

1141 **Tell your healthcare provider about all your medical 1142 conditions, including if you:**

- 1143 • have tendon problems
- 1144 • have central nervous system problems (such as epilepsy)
- 1145 • have nerve problems
- 1146 • have or anyone in your family has an irregular heartbeat, especially a condition called “QT
 1147 prolongation”
- 1148 • have low blood potassium (hypokalemia)
- 1149 • have a slow heartbeat (bradycardia)
- 1150 • have a history of seizures
- 1151 • have kidney problems
- 1152 • have rheumatoid arthritis (RA) or other history of joint problems
- 1153 • are pregnant or planning to become pregnant. It is not known if AVELOX will harm your
 1154 unborn child.

- 1155 • are breast-feeding or planning to breast-feed. It is not known if AVELOX passes into breast
 1156 milk. You and your healthcare provider should decide whether you will take AVELOX or
 1157 breast-feed.

1158 **Tell your healthcare provider about all the medicines you take**, including prescription and
 1159 non-prescription medicines, vitamins and herbal and dietary supplements. AVELOX and other
 1160 medicines can affect each other causing side effects. Especially tell your healthcare provider if
 1161 you take:

- 1162 • an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain
 1163 relief are NSAIDs. Taking an NSAID while you take AVELOX or other fluoroquinolones
 1164 may increase your risk of central nervous system effects and seizures. See “**What are the
 1165 possible side effects of AVELOX?**”
- 1166 • a blood thinner (warfarin, Coumadin, Jantoven)
- 1167 • a medicine to control your heart rate or rhythm (antiarrhythmic) See “**What are the
 1168 possible side effects of AVELOX?**”
- 1169 • an anti-psychotic medicine
- 1170 • a tricyclic antidepressant
- 1171 • erythromycin
- 1172 • a water pill (diuretic)
- 1173 • a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance
 1174 of tendon injury. See “**What is the most important information I should know about
 1175 AVELOX?**”
- 1176 • Certain medicines may keep AVELOX from working correctly. Take AVELOX either 4
 1177 hours before or 8 hours after taking these products:
 - 1178 • an antacid, multivitamin, or other product that has magnesium, aluminum, iron, or zinc
 - 1179 • sucralfate (Carafate)
 - 1180 • didanosine (Videx[®], Videx EC[®])

1181 Ask your healthcare provider if you are not sure if any of your
 1182 medicines are listed above.

1183 Know the medicines you take. Keep a list of your medicines and show it to your healthcare
 1184 provider and pharmacist when you get a new medicine.

1185 **How should I take AVELOX?**

- 1186 • Take AVELOX once a day exactly as prescribed by your healthcare provider.
- 1187 • Take AVELOX at about the same time each day.
- 1188 • AVELOX Tablets should be swallowed.
- 1189 • AVELOX can be taken with or without food.
- 1190 • Drink plenty of fluids while taking AVELOX.
- 1191 • AVELOX I.V. is given to you by intravenous (I.V.) infusion into your vein slowly, over 60
 1192 minutes, as prescribed by your healthcare provider.
- 1193 • Do not skip any doses, or stop taking AVELOX even if you begin to feel better, until you
 1194 finish your prescribed treatment, unless:
 - 1195 • you have tendon effects (see “**What is the most important information I should
 1196 know about AVELOX?**”),

- 1197 • you have a serious allergic reaction (see “**What are the possible side effects of**
 1198 **AVELOX?**”), or
 1199 • your healthcare provider tells you to stop.
 1200 This will help make sure that all of the bacteria are killed and lower the chance that the
 1201 bacteria will become resistant to AVELOX. If this happens, AVELOX and other antibiotic
 1202 medicines may not work in the future.
 1203 • If you miss a dose of AVELOX, take it as soon as you remember. Do not take more than 1
 1204 dose of AVELOX in one day.
 1205 • If you take too much, call your healthcare provider or get medical help immediately.

1206 **What should I avoid while taking AVELOX?**

- 1207 • AVELOX can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do
 1208 other activities that require mental alertness or coordination until you know how AVELOX
 1209 affects you.
 1210 • Avoid sunlamps, tanning beds, and try to limit your time in the sun. AVELOX can make
 1211 your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning
 1212 beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these
 1213 symptoms while taking AVELOX, call your healthcare provider right away. You should
 1214 use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

1215 **What are the possible side effects of AVELOX?**

- 1216 • AVELOX can cause side effects that may be serious or even cause death. See “**What is the**
 1217 **most important information I should know about AVELOX?**”

1218 Other serious side effects of AVELOX include:

- 1219 • **Central Nervous System effects**
 1220 Seizures have been reported in people who take fluoroquinolone antibiotics including
 1221 AVELOX. Tell your healthcare provider if you have a history of seizures. Ask your
 1222 healthcare provider whether taking AVELOX will change your risk of having a seizure.
 1223 Central Nervous System (CNS) side effects may happen as soon as after taking the first
 1224 dose of AVELOX. Talk to your healthcare provider right away if you have any of these side
 1225 effects, or other changes in mood or behavior:
 1226 • feeling dizzy
 1227 • seizures
 1228 • hear voices, see things, or sense things that are not there (hallucinations)
 1229 • feel restless
 1230 • tremors
 1231 • feel anxious or nervous
 1232 • confusion
 1233 • depression
 1234 • trouble sleeping
 1235 • feel more suspicious (paranoia)
 1236 • suicidal thoughts or acts
 1237 • nightmares
 1238 • **Serious allergic reactions**

- 1239 Allergic reactions can happen in people taking fluoroquinolones, including AVELOX,
 1240 even after only one dose. Stop taking AVELOX and get emergency medical help right
 1241 away if you get any of the following symptoms of a severe allergic reaction:
- 1242 • hives
 - 1243 • trouble breathing or swallowing
 - 1244 • swelling of the lips, tongue, face
 - 1245 • throat tightness, hoarseness
 - 1246 • rapid heartbeat
 - 1247 • faint
 - 1248 • yellowing of the skin or eyes. Stop taking AVELOX and tell your healthcare provider
 1249 right away if you get yellowing of your skin or white part of your eyes, or if you have
 1250 dark urine. These can be signs of a serious reaction to AVELOX (a liver problem).
- 1251 • **Skin rash**
 1252 Skin rash may happen in people taking AVELOX even after only one dose. Stop taking
 1253 AVELOX at the first sign of a skin rash and call your healthcare provider. Skin rash may be
 1254 a sign of a more serious reaction to AVELOX.
 - 1255 • **Serious heart rhythm changes** (QT prolongation and torsade de pointes)
 1256 Tell your healthcare provider right away if you have a change in your heart beat (a fast or
 1257 irregular heartbeat), or if you faint. AVELOX may cause a rare heart problem known as
 1258 prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be
 1259 very dangerous. The chances of this event are higher in people:
 - 1260 • who are elderly
 - 1261 • with a family history of prolonged QT interval
 - 1262 • with low blood potassium (hypokalemia)
 - 1263 • who take certain medicines to control heart rhythm (antiarrhythmics)
 - 1264 • **Intestine infection** (Pseudomembranous colitis)
 1265 Pseudomembranous colitis can happen with most antibiotics, including AVELOX. Call
 1266 your healthcare provider right away if you get watery diarrhea, diarrhea that does not go
 1267 away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous
 1268 colitis can happen 2 or more months after you have finished your antibiotic.
 - 1269 • **Changes in sensation and possible nerve damage** (Peripheral Neuropathy)
 1270 Damage to the nerves in arms, hands, legs, or feet can happen in people taking
 1271 fluoroquinolones, including AVELOX. Talk with your healthcare provider right away if
 1272 you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs,
 1273 or feet:
 - 1274 • pain
 - 1275 • burning
 - 1276 • tingling
 - 1277 • numbness
 - 1278 • weakness
- 1279 AVELOX may need to be stopped to prevent permanent nerve damage.
- 1280 • **Sensitivity to sunlight** (photosensitivity)
 1281 See “**What should I avoid while taking AVELOX?**”

1282 The most common side effects of AVELOX include nausea and diarrhea.
 1283 These are not all the possible side effects of AVELOX. Tell your healthcare provider about any
 1284 side effect that bothers you or that does not go away.
 1285 Call your doctor for medical advice about side effects. You may report side effects to FDA at
 1286 1-800-FDA-1088.

1287 **How should I store AVELOX?**

1288 **AVELOX Tablets**

- 1289 • Store AVELOX 59–86°F (15–30°C)
- 1290 • Keep AVELOX away from moisture (humidity)

1291 **Keep AVELOX and all medicines out of the reach of children.**

1292 **General Information about AVELOX**

1293 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
 1294 Do not use AVELOX for a condition for which it is not prescribed. Do not give AVELOX to
 1295 other people, even if they have the same symptoms that you have. It may harm them.
 1296 This Medication Guide summarizes the most important information about AVELOX. If you
 1297 would like more information about AVELOX, talk with your healthcare provider. You can ask
 1298 your healthcare provider or pharmacist for information about AVELOX that is written for
 1299 healthcare professionals. For more information go to www.AVELOX.com or call
 1300 1-800-526-4099.

1301 **What are the ingredients in AVELOX?**

- 1302 • **AVELOX Tablets:**
 - 1303 • Active ingredient: moxifloxacin hydrochloride
 - 1304 • Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose
 - 1305 sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, and
 - 1306 ferric oxide
- 1307 • **AVELOX I.V.:**
 - 1308 • Active ingredient: moxifloxacin hydrochloride
 - 1309 • Inactive ingredients: sodium chloride, USP, water for injection, USP, and may include
 - 1310 hydrochloric acid and/or sodium hydroxide for pH adjustment

1311 Revised October 2008

1312 This Medication Guide has been approved by the U.S. Food and Drug
 1313 Administration. Manufactured by:



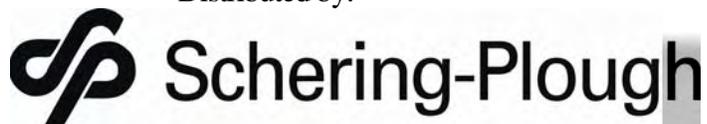
1314 **Bayer HealthCare
Pharmaceuticals**

1315 Bayer HealthCare Pharmaceuticals Inc.
 1316 Wayne, NJ 07470

1317
 1318 Avelox Tablets made in Germany

1319 Avelox I.V. made in Germany
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