

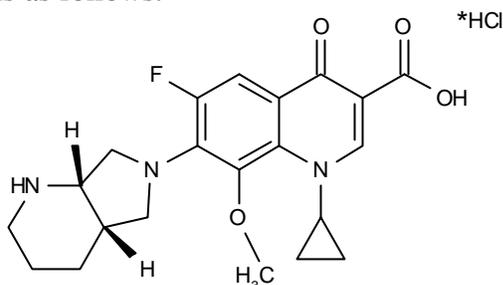
1 **AVELOX<sup>®</sup> (moxifloxacin hydrochloride) Tablets**  
2 **AVELOX<sup>®</sup> I.V. (moxifloxacin hydrochloride in sodium chloride injection)**

4 **FINAL DRAFT PACKAGE INSERT**

**5/02**

5  
6 **DESCRIPTION**

7 AVELOX<sup>®</sup> (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and  
8 is available as AVELOX Tablets for oral administration and as AVELOX I.V. for intravenous  
9 administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of  
10 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-  
11 3-quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a  
12 molecular weight of 437.9. Its empirical formula is C<sub>21</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>4</sub> \*HCl and its chemical structure  
13 is as follows:



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

20  
21 AVELOX I.V. is available in ready-to-use 250 mL latex-free flexibags as a sterile, preservative  
22 free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg  
23 moxifloxacin) with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is  
24 yellow. The color does not affect, nor is it indicative of, product stability. The inactive  
25 ingredients are sodium chloride, USP, water for Injection, USP, and may include hydrochloric  
26 acid and/or sodium hydroxide for pH adjustment.

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## CLINICAL PHARMACOLOGY

### Absorption

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

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

The mean ( $\pm$  SD)  $C_{max}$  and AUC values following single and multiple doses of 400 mg moxifloxacin given orally are summarized below.

	<b>Cmax (mg/L)</b>	<b>AUC (mg· h/L)</b>	<b>Half-life (hr)</b>
Single Dose Oral Healthy (n = 372)	3.1 $\pm$ 1.0	36.1 $\pm$ 9.1	11.5 - 15.6*
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 $\pm$ 0.5	48.0 $\pm$ 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 $\pm$ 9.0	
Healthy young female (n = 9)	4.2 $\pm$ 0.5	49.3 $\pm$ 9.5	
* Range of means from different studies			

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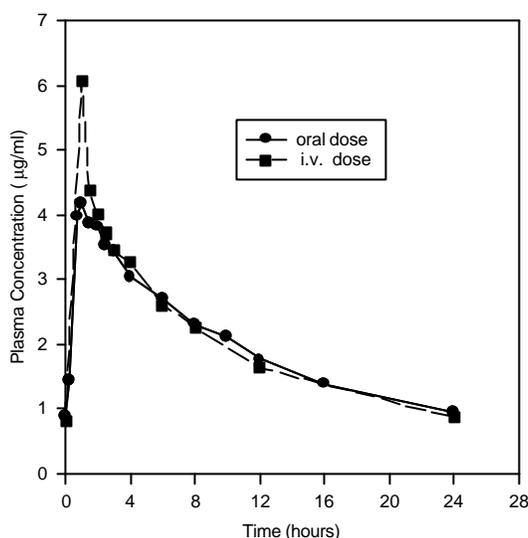
The mean ( $\pm$  SD)  $C_{max}$  and AUC values following single and multiple doses of 400 mg moxifloxacin given by 1 hour i.v. infusion are summarized below.

	<b>Cmax (mg/L)</b>	<b>AUC (mg· h/L)</b>	<b>Half-life (hr)</b>
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 $\pm$ 2.0		
< 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	38.0 $\pm$ 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		
* Range of means from different studies			
** Expected Cmax (concentration obtained around the time of the end of the infusion)			

44

45 Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg  
46 single oral dose). The mean ( $\pm$  SD) elimination half-life from plasma is  $12 \pm 1.3$  hours; steady-  
47 state is achieved after at least three days with a 400 mg once daily regimen.  
48  
49

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



50 **Distribution**

51 Moxifloxacin is approximately 50% bound to serum proteins, independent of drug concentration.  
52 The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg. Moxifloxacin is widely  
53 distributed throughout the body, with tissue concentrations often exceeding plasma  
54 concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions,  
55 mucosa of the sinuses, skin blister fluid, and subcutaneous tissue, and skeletal muscle following  
56 oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are  
57 summarized in the following table. The rates of elimination of moxifloxacin from tissues  
58 generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) After Oral Dosing in Plasma and Tissues Measured 3 Hours After Dosing with 400 mg <sup>§</sup>				
Tissue or Fluid	N	Plasma Concentration (mg/mL)	Tissue or Fluid Concentration (mg/mL or mg/g)	Tissue Plasma Ratio:
<b>Respiratory</b>				
Alveolar Macrophages	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
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
<b>Sinus</b>				
Maxillary Sinus Mucosa	4	3.7 ± 1.1 <sup>†</sup>	7.6 ± 1.7	2.0 ± 0.3
Anterior Ethmoid Mucosa	3	3.7 ± 1.1 <sup>†</sup>	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	3.7 ± 1.1 <sup>†</sup>	9.8 ± 4.5	2.6 ± 0.6

<sup>§</sup> all moxifloxacin concentrations were measured after a single 400 mg dose, except the sinus concentrations which were measured after 5 days of dosing.

<sup>†</sup>N = 5

59

## 60 **Metabolism**

61 Moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450  
62 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The  
63 sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily  
64 in the feces. Approximately 14% of an oral or intravenous dose is converted to a glucuronide  
65 conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2  
66 are approximately 40% those of the parent drug, while plasma concentrations of M1 are  
67 generally less than 10% those of moxifloxacin.

68

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

72

## 73 **Excretion**

74 Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged  
75 drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as  
76 either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance  
77 and renal clearance are 12 ± 2.0 L/hr and 2.6 ± 0.5 L/hr, respectively.

78

## 79 **Special Populations**

### 80 **Geriatric**

81 Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8  
82 female) and 16 young (8 male; 8 female) healthy volunteers, there were no age-related changes  
83 in moxifloxacin pharmacokinetics. In 16 healthy elderly male and female volunteers (66-81  
84 years of age) given a single 200 mg dose of oral moxifloxacin, the extent of systemic exposure  
85 (AUC and C<sub>max</sub>) was not statistically different between young and elderly males and elimination  
86 half-life was unchanged. No dosage adjustment is necessary based on age. In large phase III  
87 studies, the concentrations around the time of the end of the infusion in elderly patients following  
88 intravenous infusion of 400 mg were similar to those observed in young patients.

89

### 90 **Pediatric**

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

92

### 93 **Gender**

94 Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-  
95 75 years) and 24 healthy females (19-70 years), the mean AUC and  $C_{max}$  were 8% and 16%  
96 higher, respectively, in females compared to males. There are no significant differences in  
97 moxifloxacin pharmacokinetics between male and female subjects when differences in body  
98 weight are taken into consideration.

99

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

104

### 105 **Race**

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

109

### 110 **Renal Insufficiency**

111 The pharmacokinetic parameters of moxifloxacin are not significantly altered by mild, moderate,  
112 or severe renal impairment. No dosage adjustment is necessary in patients with renal impairment.

113

114 In a single oral dose study of 24 patients with varying degrees of renal function from normal to  
115 severely impaired, the mean peak concentrations ( $C_{max}$ ) of moxifloxacin were reduced by 22%  
116 and 21% in the patients with moderate ( $\text{CL}_{CR} \geq 30$  and  $\leq 60$  mL/min) and severe ( $\text{CL}_{CR} <$   
117  $30\text{mL/min}$ ) renal impairment, respectively. The mean systemic exposure (AUC) in these  
118 patients was increased by 13%. In the moderate and severe renally impaired patients, the mean  
119 AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean  
120 AUC and  $C_{max}$  for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-  
121 fold) and 1.4-fold (ranging up to 2.5-fold), respectively. The sulfate and glucuronide conjugates  
122 are not microbiologically active, and the clinical implication of increased exposure to these  
123 metabolites in patients with renal impairment has not been studied.

124

125 The effect of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) on the  
126 pharmacokinetics of moxifloxacin has not been studied.

127

### 128 **Hepatic Insufficiency**

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

133

134 The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up  
135 to 5.9-fold) and 5.7-fold (ranging up to 8.0-fold) in the mild and moderate groups, respectively.  
136 The mean  $C_{max}$  of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and  
137 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-  
138 fold (ranging up to 2.5-fold) in both groups. The mean  $C_{max}$  of M2 increased by 1.6- and 1.3-fold  
139 (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to  
140 the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is  
141 recommended for mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The  
142 pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not  
143 been studied. (See **DOSAGE AND ADMINISTRATION**.)  
144

### 145 **Photosensitivity Potential**

146 A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32  
147 healthy volunteers (8 per group) demonstrated that moxifloxacin does not show phototoxicity in  
148 comparison to placebo. The minimum erythematous dose (MED) was measured before and after  
149 treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily),  
150 or placebo. In this study, the MED measured for both doses of moxifloxacin were not  
151 significantly different from placebo, while lomefloxacin significantly lowered the MED. (See  
152 **PRECAUTIONS, Information for Patients**.)  
153

### 154 **Drug-drug Interactions**

155 The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole,  
156 theophylline, warfarin, digoxin, probenecid, morphine, oral contraceptive, ranitidine, glyburide,  
157 calcium, iron, and antacids has been evaluated. There was no clinically significant effect of  
158 moxifloxacin on itraconazole, theophylline, warfarin, digoxin, oral contraceptives, or glyburide  
159 kinetics. Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine, and  
160 calcium did not significantly affect the pharmacokinetics of moxifloxacin. These results and the  
161 data from *in vitro* studies suggests that moxifloxacin is unlikely to significantly alter the  
162 metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19, or  
163 CYP1A2 enzymes.  
164

165 As with all other quinolones, iron and antacids significantly reduced bioavailability of  
166 moxifloxacin.  
167

168 **Itraconazole:** In a study involving 11 healthy volunteers, there was no significant effect of  
169 itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the  
170 pharmacokinetics of moxifloxacin (a single 400 mg dose given on the 7<sup>th</sup> day of itraconazole  
171 dosing). In addition, moxifloxacin was shown not to affect the pharmacokinetics of itraconazole.  
172

173 **Theophylline:** No significant effect of moxifloxacin (200 mg every twelve hours for 3 days) on  
174 the pharmacokinetics of theophylline (400 mg every twelve hours for 3 days) was detected in a  
175 study involving 12 healthy volunteers. In addition, theophylline was not shown to affect the  
176 pharmacokinetics of moxifloxacin. The effect of co-administration of a 400 mg dose of  
177 moxifloxacin with theophylline has not been studied, but it is not expected to be clinically  
178 significant based on *in vitro* metabolic data showing that moxifloxacin does not inhibit the  
179 CYP1A2 isoenzyme.  
180

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

185  
186 **Digoxin:** No significant effect of moxifloxacin (400 mg once daily for two days) on digoxin  
187 (0.6 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The  
188 mean digoxin  $C_{max}$  increased by about 50% during the distribution phase of digoxin. This  
189 transient increase in digoxin  $C_{max}$  is not viewed to be clinically significant. Moxifloxacin  
190 pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for  
191 moxifloxacin or digoxin is required when these drugs are administered concomitantly.

192  
193 **Morphine:** No significant effect of morphine sulfate (a single 10 mg intramuscular dose) on the  
194 mean AUC and  $C_{max}$  of moxifloxacin (400 mg single dose) was observed in a study of 20 healthy  
195 male and female volunteers.

196  
197 **Oral Contraceptives:** A placebo-controlled study in 29 healthy female subjects showed that  
198 Moxifloxacin 400 mg daily for 7 days did not interfere with the hormonal suppression of oral  
199 contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum  
200 progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered  
201 contraceptive agents.

202  
203 **Probenecid:** Probenecid (500 mg twice daily for two days) did not alter the renal clearance and  
204 total amount of moxifloxacin (400 mg single dose) excreted renally in a study of 12 healthy  
205 volunteers.

206  
207 **Ranitidine:** No significant effect of ranitidine (150 mg twice daily for three days as  
208 pretreatment) on the pharmacokinetics of moxifloxacin (400 mg single dose) was detected in a  
209 study involving 10 healthy volunteers.

210  
211 **Antidiabetic agents:** In diabetics, glyburide (2.5 mg once daily for two weeks pretreatment  
212 and for five days concurrently) mean AUC and  $C_{max}$  were 12% and 21 % lower, respectively,  
213 when taken with moxifloxacin (400 mg once daily for five days) in comparison to placebo.  
214 Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and  
215 moxifloxacin in comparison to those taking glyburide alone, suggesting no interference by  
216 moxifloxacin on the activity of glyburide. These interaction results are not viewed as clinically  
217 significant.

218  
219 **Calcium:** Twelve healthy volunteers were administered concomitant moxifloxacin (single 400  
220 mg dose) and calcium (single dose of 500 mg  $Ca^{++}$  dietary supplement) followed by an  
221 additional two doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had  
222 no significant effect on the mean AUC of moxifloxacin. The mean  $C_{max}$  was slightly reduced  
223 and the time to maximum plasma concentration was prolonged when moxifloxacin was given  
224 with calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours).  
225 These differences are not considered to be clinically significant.

226

227 **Antacids:** When moxifloxacin (single 400 mg tablet dose) was administered two hours before,  
228 concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum  
229 hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there  
230 was a 26%, 60% and 23% reduction in the mean AUC of moxifloxacin, respectively.  
231 Moxifloxacin should be taken at least 4 hours before or 8 hours after antacids containing  
232 magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin  
233 preparations with zinc, or Videx<sup>®</sup> (didanosine) chewable/buffered tablets or the pediatric powder  
234 for oral solution. (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND**  
235 **ADMINISTRATION.**)  
236

237 **Iron:** When moxifloxacin tablets were administered concomitantly with iron (ferrous sulfate  
238 100 mg once daily for two days), the mean AUC and C<sub>max</sub> of moxifloxacin was reduced by 39%  
239 and 59%, respectively. Moxifloxacin should only be taken more than 4 hours before or 8 hours  
240 after iron products. (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND**  
241 **ADMINISTRATION.**)  
242

243 **Electrocardiogram:** Prolongation of the QT interval in the ECG has been observed in some  
244 patients receiving moxifloxacin. Following oral dosing with 400 mg of moxifloxacin the mean  
245 ( $\pm$  SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6  
246 msec ( $\pm$  26) (n=787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion  
247 each day) the mean change in QTc from the Day 1 pre-dose value was 9 msec ( $\pm$  24) on Day 1 (n  
248 = 69) and 3 msec ( $\pm$  29) on Day 3 (n = 290). (See **WARNINGS.**)  
249

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

## 257 **MICROBIOLOGY**

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

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

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

274  
275 Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against  
276 Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may,  
277 however, still be susceptible to moxifloxacin.

278  
279 Moxifloxacin has been shown to be active against most strains of the following microorganisms,  
280 both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE**  
281 section.

282

### 283 **Aerobic Gram-positive microorganisms**

284

285 *Staphylococcus aureus* (methicillin-susceptible strains only)  
286 *Streptococcus pneumoniae* (penicillin-susceptible strains only)  
287 *Streptococcus pyogenes*

288

### 289 **Aerobic Gram-negative microorganisms**

290

291 *Haemophilus influenzae*  
292 *Haemophilus parainfluenzae*  
293 *Klebsiella pneumoniae*  
294 *Moraxella catarrhalis*

295

### 296 **Other microorganisms**

297

298 *Chlamydia pneumoniae*  
299 *Mycoplasma pneumoniae*

300

301 The following *in vitro* data are available, **but their clinical significance is unknown.**

302

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

### 307 **Aerobic Gram-positive microorganisms**

308

309 *Staphylococcus epidermidis* (methicillin-susceptible strains only)  
310 *Streptococcus agalactiae*  
311 *Streptococcus pneumoniae* (penicillin-resistant strains)  
312 *Streptococcus viridans* group

313



355

356 For testing *Streptococcus* species including *Streptococcus pneumoniae*<sup>b</sup>:

357

358 **MIC (mg/mL)**

**Interpretation**

359

360 ≤ 1.0 Susceptible (S)

361 2.0 Intermediate (I)

362 ≥ 4.0 Resistant (R)

363

364 <sup>b</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests using  
365 cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

366

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

377

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

381

382 **Microorganism**

**MIC (µg/mL)**

383

384 *Enterococcus faecalis* ATCC 29212 0.06 - 0.5

385 *Escherichia coli* ATCC 25922 0.008 - 0.06

386 *Haemophilus influenzae* ATCC 49247<sup>c</sup> 0.008 - 0.03

387 *Staphylococcus aureus* ATCC 29213 0.015 - 0.06

388 *Streptococcus pneumoniae* ATCC 49619<sup>d</sup> 0.06 - 0.25

389

390 <sup>c</sup> This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth  
391 microdilution procedure using *Haemophilus* Test Medium (HTM)<sup>1</sup>.

392 <sup>d</sup> This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth  
393 microdilution procedure using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse  
394 blood.

395

396 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters also  
397 provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One  
398 such standardized procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This  
399 procedure uses paper disks impregnated with 5-µg moxifloxacin to test the susceptibility of  
400 microorganisms to moxifloxacin.

401 Reports from the laboratory providing results of the standard single-disk susceptibility test with a  
402 5-µg moxifloxacin disk should be interpreted according to the following criteria:  
403 The following zone diameter interpretive criteria should be used for testing Enterobacteriaceae  
404 and *Staphylococcus* species:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
408 ≥ 19	Susceptible (S)
409 16 - 18	Intermediate (I)
410 ≤ 15	Resistant (R)

411 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>e</sup>:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
416 ≥ 18	Susceptible (S)

417 <sup>e</sup> This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and  
418 *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

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

423 For testing *Streptococcus* species including *Streptococcus pneumoniae*<sup>f</sup>:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
428 ≥ 18	Susceptible (S)
430 15 - 17	Intermediate (I)
431 ≤ 14	Resistant (R)

432 <sup>f</sup> These interpretive standards are applicable only to disk diffusion tests using Mueller-Hinton  
433 agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.

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

436 As with standardized dilution techniques, diffusion methods require the use of laboratory control  
437 microorganisms that are used to control the technical aspects of the laboratory procedures. For  
438 the diffusion technique, the 5-µg moxifloxacin disk should provide the following zone diameters  
439 in these laboratory test quality control strains:  
440  
441

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>	
442			
443			
444	<i>Escherichia coli</i>	ATCC 25922	28 - 35
445	<i>Haemophilus influenzae</i>	ATCC 49247 <sup>g</sup>	31 – 39

446	<i>Staphylococcus aureus</i>	ATCC 25923	28 – 35
447	<i>Streptococcus pneumoniae</i>	ATCC 49619 <sup>h</sup>	25 – 31

448

449 <sup>g</sup>These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using  
450 *Haemophilus* Test Medium (HTM)<sup>2</sup>.

451

452 <sup>h</sup> These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC  
453 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5%  
454 defibrinated sheep blood.

455

#### 456 **INDICATIONS AND USAGE**

457 AVELOX Tablets and I.V. are indicated for the treatment of adults ( $\geq$  18 years of age) with  
458 infections caused by susceptible strains of the designated microorganisms in the conditions listed  
459 below. (See **DOSAGE AND ADMINISTRATION** for specific recommendations. In addition,  
460 for I.V. use see **PRECAUTIONS, Geriatric Use**.)

461

462 **Acute Bacterial Sinusitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or  
463 *Moraxella catarrhalis*.

464

465 **Acute Bacterial Exacerbation of Chronic Bronchitis** caused by *Streptococcus*  
466 *pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*,  
467 *Staphylococcus aureus*, or *Moraxella catarrhalis*.

468

469 **Community Acquired Pneumonia** caused by *Streptococcus pneumoniae*, *Haemophilus*  
470 *influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma*  
471 *pneumoniae*, or *Chlamydia pneumoniae*.

472

473 **Uncomplicated Skin and Skin Structure Infections** caused by *Staphylococcus aureus* or  
474 *Streptococcus pyogenes*.

475

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

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#### 481 **CONTRAINDICATIONS**

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

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**WARNINGS**

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

**Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.**

Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 7900 patients in controlled clinical studies, including 223 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 moxifloxacin tablet treated patients in a post-marketing observational study in which ECGs were not performed. (See **CLINICAL PHARMACOLOGY, Electrocardiogram**. For I.V. use see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS, Geriatric Use**.)

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving moxifloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, moxifloxacin should be used with

530 caution in patients with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis,  
531 epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the  
532 seizure threshold. (See **PRECAUTIONS: General, Information for Patients**, and  
533 **ADVERSE REACTIONS**.)

534  
535 Serious anaphylactic reactions, some following the first dose, have been reported in patients  
536 receiving quinolone therapy, including moxifloxacin. Some reactions were accompanied by  
537 cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea,  
538 urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment  
539 with epinephrine. Moxifloxacin should be discontinued at the first appearance of a skin rash or  
540 any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management,  
541 including intubation, may be administered as indicated.

542  
543 Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain etiology,  
544 have been reported in patients receiving therapy with all antibiotics. These events may be severe  
545 and generally occur following the administration of multiple doses. Clinical manifestations may  
546 include one or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

547  
548 **Pseudomembranous colitis has been reported with nearly all antibacterial agents and may**  
549 **range in severity from mild to life-threatening. Therefore, it is important to consider this**  
550 **diagnosis in patients who present with diarrhea subsequent to the administration of**  
551 **antibacterial agents.**

552  
553 Treatment with antibacterial agents alters the normal flora of the colon and may permit  
554 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one  
555 primary cause of “antibiotic-associated colitis.”

556  
557 After the diagnosis of pseudomembranous colitis has been established, therapeutic measures  
558 should be initiated. Mild cases of pseudomembranous colitis usually respond to drug  
559 discontinuation alone. In moderate to severe cases, consideration should be given to  
560 management with fluids and electrolytes, protein supplementation, and treatment with an  
561 antibacterial drug clinically effective against *C. difficile* colitis.

562  
563 Although not observed in moxifloxacin clinical trials, Achilles and other tendon ruptures that  
564 required surgical repair or resulted in prolonged disability have been reported with quinolones.  
565 Post-marketing surveillance reports indicate that the risk may be increased in patients receiving  
566 concomitant corticosteroids, especially in the elderly. Moxifloxacin should be discontinued if the  
567 patient experiences pain, inflammation, or rupture of a tendon.

## 568 **PRECAUTIONS**

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

573

574 **Information for Patients:**

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

577

578 Patients should be advised:

579

- 580 ◆ that moxifloxacin may produce changes in the electrocardiogram (QTc interval  
581 prolongation).
- 582 ◆ that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine,  
583 procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- 584 ◆ that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride,  
585 erythromycin, antipsychotics, and tricyclic antidepressants.
- 586 ◆ to inform their physician of any personal or family history of QTc prolongation or  
587 proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute  
588 myocardial ischemia.
- 589 ◆ to inform their physician of any other medications when taken concurrently with  
590 moxifloxacin, including over-the-counter medications.
- 591 ◆ to contact their physician if they experience palpitations or fainting spells while taking  
592 moxifloxacin.
- 593 ◆ that moxifloxacin tablets may be taken with or without meals, and to drink fluids liberally.
- 594 ◆ that moxifloxacin tablets should be taken at least 4 hours before or 8 hours after  
595 multivitamins (containing iron or zinc), antacids (containing magnesium or aluminum),  
596 sucralfate, or Videx<sup>®</sup> (didanosine) chewable/buffered tablets or the pediatric powder for oral  
597 solution. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and  
598 **PRECAUTIONS, Drug Interactions**.)
- 599 ◆ that moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic  
600 reactions, even following a single dose, and to discontinue the drug at the first sign of a skin  
601 rash or other signs of an allergic reaction.
- 602 ◆ to discontinue treatment; rest and refrain from exercise; and inform their physician if they  
603 experience pain, inflammation, or rupture of a tendon.
- 604 ◆ that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know  
605 how they react to this drug before they operate an automobile or machinery or engage in  
606 activities requiring mental alertness or coordination.
- 607 ◆ that phototoxicity has been reported in patients receiving certain quinolones. There was no  
608 phototoxicity seen with moxifloxacin at the recommended dose. In keeping with good  
609 medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If  
610 sunburn-like reaction or skin eruptions occur, contact your physician. (See **CLINICAL  
611 PHARMACOLOGY, Photosensitivity Potential**.)
- 612 ◆ that convulsions have been reported in patients receiving quinolones, and they should notify  
613 their physician before taking this drug if there is a history of this condition.

614

615 **Drug Interactions:**

616 Antacids, Sucralfate, Metal Cations, Multivitamins: Quinolones form chelates with alkaline  
617 earth and transition metal cations. Oral administration of quinolones with antacids containing  
618 aluminum or magnesium with sucralfate, with metal cations such as iron, or with multivitamins  
619 containing iron or zinc, or with formulations containing divalent and trivalent cations such as  
620 Videx<sup>®</sup> (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may  
621 substantially interfere with the absorption of quinolones, resulting in systemic concentrations  
622 considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before  
623 or 8 hours after these agents. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and  
624 **DOSAGE AND ADMINISTRATION.**)

625

626 No clinically significant drug-drug interactions between itraconazole, theophylline, warfarin,  
627 digoxin, oral contraceptives or glyburide have been observed with moxifloxacin. Itraconazole,  
628 theophylline, digoxin, probenecid, morphine, ranitidine, and calcium have been shown not to  
629 significantly alter the pharmacokinetics of moxifloxacin. (See **CLINICAL**  
630 **PHARMACOLOGY.**)

631

632 Warfarin: No significant effect of moxifloxacin on R- and S-warfarin was detected in a clinical  
633 study involving 24 healthy volunteers. No significant changes in prothrombin time were noted  
634 in the presence of moxifloxacin. However, since some quinolones have been reported to  
635 enhance the anticoagulant effects of warfarin or its derivatives in the patient population, the  
636 prothrombin time or other suitable coagulation test should be closely monitored if a quinolone  
637 antimicrobial is administered concomitantly with warfarin or its derivatives.

638

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

643

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

648

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

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

652

653 Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used  
654 in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response  
655 observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition  
656 of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene  
657 mutation assay. An equivocal result was obtained in the same assay when v79 cells were used.  
658 Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce

659 unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity  
660 *in vivo* in a micronucleus test or a dominant lethal test in mice.

661

662 Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500  
663 mg/kg/day, approximately 12 times the maximum recommended human dose based on body  
664 surface area ( $\text{mg}/\text{m}^2$ ), or at intravenous doses as high as 45 mg/kg/day, approximately equal to  
665 the maximum recommended human dose based on body surface area ( $\text{mg}/\text{m}^2$ ). At 500 mg/kg  
666 orally there were slight effects on sperm morphology (head-tail separation) in male rats and on  
667 the estrous cycle in female rats.

668

### 669 **Pregnancy: Teratogenic Effects. Pregnancy Category C:**

670 Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at  
671 oral doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose  
672 based on systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal  
673 skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 80  
674 mg/kg/day (approximately 2 times the maximum recommended human dose based on body  
675 surface area ( $\text{mg}/\text{m}^2$ )) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal  
676 and placental weights and the appearance of the placenta. There was no evidence of  
677 teratogenicity at intravenous doses as high as 80 mg/kg/day. Intravenous administration of 20  
678 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon  
679 systemic exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body  
680 weights and delayed fetal skeletal ossification. When rib and vertebral malformations were  
681 combined, there was an increased fetal and litter incidence of these effects. Signs of maternal  
682 toxicity in rabbits at this dose included mortality, abortions, marked reduction of food  
683 consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence  
684 of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100  
685 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure).  
686 An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and  
687 postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight  
688 increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased  
689 neonatal survival. Treatment-related maternal mortality occurred during gestation at 500  
690 mg/kg/day in this study.

691

692 Since there are no adequate or well-controlled studies in pregnant women, moxifloxacin should  
693 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

694

### 695 **Nursing Mothers:**

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

700

### 701 **Pediatric Use:**

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

704

705 **Geriatric Use:**

706 In controlled multiple-dose clinical trials, 23% of patients receiving oral moxifloxacin were  
707 greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The  
708 clinical trial data demonstrate that there is no difference in the safety and efficacy of oral  
709 moxifloxacin in patients aged 65 or older compared to younger adults.

710

711 In intravenous trials in community acquired pneumonia, 45% of moxifloxacin patients were  
712 greater than or equal to 65 years of age, and 24% were greater than or equal to 75 years of age.  
713 In the pool of 491 elderly ( $\geq 65$  years) patients, the following ECG abnormalities were reported  
714 in moxifloxacin vs. comparator patients: ST-T wave changes (2 events vs. 0 events), QT  
715 prolongation (2 vs. 0), ventricular tachycardia (1 vs. 0), atrial flutter (1 vs. 0), tachycardia (2 vs.  
716 1), atrial fibrillation (1 vs. 0), supraventricular tachycardia (1 vs. 0), ventricular extrasystoles (2  
717 vs. 0), and arrhythmia (0 vs. 1). None of the abnormalities was associated with a fatal outcome  
718 and a majority of these patients completed a full-course of therapy.

719

720 **ADVERSE REACTIONS**

721 Clinical efficacy trials enrolled over 7900 moxifloxacin orally and intravenously treated patients,  
722 of whom over 6700 patients received the 400 mg dose. Most adverse events reported in  
723 moxifloxacin trials were described as mild to moderate in severity and required no treatment.  
724 Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 3.6% of  
725 orally treated patients and 5.7 % of sequentially (intravenous followed by oral) treated patients.  
726 The latter studies were conducted in community acquired pneumonia with, in general, a sicker  
727 patient population compared to the tablet studies.

728

729 Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in  
730 greater than or equal to 3% of moxifloxacin treated patients were: nausea (7%), diarrhea (6%),  
731 dizziness (3%).

732

733 Additional clinically relevant uncommon events, judged by investigators to be at least possibly  
734 drug-related, that occurred in greater than or equal to 0.1% and less than 3% of moxifloxacin  
735 treated patients were:

736

737 **BODY AS A WHOLE:** headache, abdominal pain, injection site reaction, asthenia, moniliasis,  
738 pain, malaise, lab test abnormal (not specified), allergic reaction, leg pain, back pain, chest pain  
739 **CARDIOVASCULAR:** palpitation, tachycardia, hypertension, peripheral edema, QT interval  
740 prolonged

741 **CENTRAL NERVOUS SYSTEM:** insomnia, nervousness, anxiety, confusion, somnolence,  
742 tremor, vertigo, paresthesia

743 **DIGESTIVE:** vomiting, abnormal liver function test, dyspepsia, dry mouth, constipation, oral  
744 moniliasis, anorexia, stomatitis, glossitis, flatulence, gastrointestinal disorder, cholestatic  
745 jaundice, GGTP increased

746 **HEMIC AND LYMPHATIC:** prothrombin decrease, thrombocythemia, thrombocytopenia,  
747 eosinophilia, leukopenia

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

749 **MUSCULOSKELETAL:** arthralgia, myalgia

750 **RESPIRATORY:** dyspnea

751 SKIN/APPENDAGES: rash (maculopapular, purpuric, pustular), pruritus, sweating

752 SPECIAL SENSES: taste perversion

753 UROGENITAL: vaginal moniliasis, vaginitis

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

756 abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis,  
757 asthma, atrial fibrillation, convulsions, depersonalization, depression, diarrhea (*Clostridium*  
758 *difficile*), dysphagia, ECG abnormal, emotional lability, face edema, gastritis, hallucinations,  
759 hyperglycemia, hyperlipidemia, hypertonia, hyperuricemia, hypesthesia, hypotension,  
760 incoordination, jaundice, kidney function abnormal, parosmia, pelvic pain, prothrombin increase,  
761 sleep disorders, speech disorders, supraventricular tachycardia, taste loss, tendon disorder,  
762 thinking abnormal, thromboplastin decrease, tinnitus, tongue discoloration, urticaria,  
763 vasodilatation, ventricular tachycardia

764

#### 765 **Post-Marketing Adverse Event Reports:**

766 Additional adverse events reported from worldwide post-marketing experience with  
767 moxifloxacin include anaphylactic reaction, anaphylactic shock, pseudomembranous colitis, and  
768 tendon rupture.

769

#### 770 **LABORATORY CHANGES**

771 Changes in laboratory parameters, without regard to drug relationship, which are not listed above  
772 and which occurred in  $\geq 2\%$  of patients and at an incidence greater than in controls included:  
773 increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin,  
774 bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose,  
775 pO<sub>2</sub>, bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities  
776 were caused by the drug or the underlying condition being treated.

777

#### 778 **OVERDOSAGE**

779 Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the  
780 event of acute overdose, the stomach should be emptied and adequate hydration maintained.  
781 ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient  
782 should be carefully observed and given supportive treatment. The administration of activated  
783 charcoal as soon as possible after oral overdose may prevent excessive increase of systemic  
784 moxifloxacin exposure. It is not known whether moxifloxacin is removed by peritoneal or  
785 hemodialysis.

786

787 Single oral moxifloxacin doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and  
788 Cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was  
789 100 mg/kg. Toxic signs after administration of a single high dose of moxifloxacin to these  
790 animals included CNS and gastrointestinal effects such as decreased activity, somnolence,  
791 tremor, convulsions, vomiting and diarrhea.

792

793 **DOSAGE AND ADMINISTRATION**

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

796

797 

Infection *	Daily Dose	Duration
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798 

Acute Bacterial Sinusitis	400 mg	10 days
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799 

Acute Bacterial Exacerbation 800 of Chronic of Bronchitis	400 mg	5 days
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801

802 

Community Acquired Pneumonia	400 mg	7-14 days
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803

804 

Uncomplicated Skin and Skin 805 Structure Infections	400 mg	7 days
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806

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

809

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

815

816 **Impaired Renal Function**

817 No dosage adjustment is required in renally impaired patients. Moxifloxacin has not been  
818 studied in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

819

820 **Impaired Hepatic Function**

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

825

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

829

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

832

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

836

837 Since only limited data are available on the compatibility of moxifloxacin intravenous injection  
838 with other intravenous substances, additives or other medications should not be added to  
839 AVELOX I.V. or infused simultaneously through the same intravenous line. If the same  
840 intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the  
841 “piggyback” method of administration is used, the line should be flushed before and after  
842 infusion of AVELOX I.V. with an infusion solution compatible with AVELOX I.V. as well as  
843 with other drug(s) administered via this common line.  
844

845 AVELOX I.V. is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:  
846

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

847

## 848 HOW SUPPLIED

848

### 849 Tablets

849

850

851 AVELOX (moxifloxacin hydrochloride) Tablets are available as oblong, dull red film-coated  
852 tablets containing 400 mg moxifloxacin. The tablet is coded with the word “BAYER” on one  
853 side and “M400” on the reverse side.  
854

854

### 855 Package

### 855 NDC Code

856

856 Bottles of 30:

0026-8581-69

857

857 Unit Dose Pack of 50:

0026-8581-88

858

858 ABC Pack of 5:

0026-8581-41

859

860 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room  
861 Temperature]. Avoid high humidity.  
862

862

### 863 Intravenous Solution – Premix Bags

864

865

865 AVELOX I.V. (moxifloxacin hydrochloride in sodium chloride injection) is available in ready-  
866 to-use 250 mL latex-free flexible bags containing 400 mg of moxifloxacin in 0.8% saline. NO  
867 FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.  
868

868

### 869 Package

### 869 NDC Code

870

870 250 mL flexible container

0026-8582-31

871

871 Parenteral drug products should be inspected visually for particulate matter prior to  
872 administration. Samples containing visible particulates should not be used.  
873

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874 Since the premix flexible containers are for single-use only, any unused portion should be  
875 discarded.  
876

876

877 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room  
878 Temperature]. **DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON**

878

879 **REFRIGERATION.**

879

880

881 **ANIMAL PHARMACOLOGY**

882 Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile  
883 dogs oral doses of moxifloxacin  $\geq$  30 mg/kg/day (approximately 1.5 times the maximum  
884 recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy.  
885 There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and  
886 500 mg/kg, respectively.

887

888 Unlike some other members of the quinolone class, crystalluria was not observed in 6 month  
889 repeat dose studies in rats and monkeys with moxifloxacin.

890

891 No ocular toxicity was observed in a 13 week oral repeat dose study in dogs with a moxifloxacin  
892 dose of 60 mg/kg. Ocular toxicity was not observed in 6 month repeat dose studies in rats and  
893 monkeys (daily oral doses up to 500mg/kg and 135mg/kg, respectively). In beagle dogs,  
894 electroretinographic (ERG) changes were observed in a 2 week study at oral doses of 60 and 90  
895 mg/kg. Histopathological changes were observed in the retina from one of four dogs at 90  
896 mg/kg, a dose associated with mortality in this study.

897

898 Some quinolones have been reported to have proconvulsant activity that is exacerbated with  
899 concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs). Moxifloxacin at an oral  
900 dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (e.g.  
901 seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or  
902 fenbufen.

903

904 In dog studies, at plasma concentrations about five times the human therapeutic level, a QT-  
905 prolonging effect of moxifloxacin was found. Electrophysiological in vitro studies suggested an  
906 inhibition of the rapid activating component of the delayed rectifier potassium current ( $I_{Kr}$ ) as an  
907 underlying mechanism. In dogs, the combined infusion of sotalol, a Class III antiarrhythmic  
908 agent, with moxifloxacin induced a higher degree of QTc prolongation than that induced by the  
909 same dose (30mg/kg) of moxifloxacin alone.

910

911 **CLINICAL STUDIES**

912 **Acute Bacterial Exacerbation of Chronic Bronchitis**

913 AVELOX Tablets (400 mg once daily for five days) were evaluated for the treatment of acute  
914 bacterial exacerbation of chronic bronchitis in a large, randomized, double-blind, controlled  
915 clinical trial conducted in the US. This study compared AVELOX with clarithromycin (500 mg  
916 twice daily for 10 days) and enrolled 629 patients. The primary endpoint for this trial was  
917 clinical success at 7-17 days post-therapy. The clinical success for AVELOX was 89%  
918 (222/250) compared to 89% (224/251) for clarithromycin.

919

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

922

<u><b>PATHOGEN</b></u>	<u><b>AVELOX</b></u>	<u><b>Clarithromycin</b></u>
923 <i>Streptococcus pneumoniae</i>	100% (16/16)	87% (20/23)
924 <i>Haemophilus influenzae</i>	89% (33/37)	88% (36/41)

925

926	<i>Haemophilus parainfluenzae</i>	100% (16/16)	100% (14/14)
927	<i>Moraxella catarrhalis</i>	85% (29/34)	100% (24/24)
928	<i>Staphylococcus aureus</i>	94% (15/16)	75% (6/8)
929	<i>Klebsiella pneumoniae</i>	90% (18/20)	91% (10/11)

930

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

935

### 936 **Community Acquired Pneumonia**

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

944

945 A large, randomized, double-blind, controlled trial was conducted in the US and Canada to  
946 compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days to an IV/PO  
947 fluoroquinolone control (trovafloxacin or levofloxacin) in the treatment of patients with  
948 clinically and radiologically documented community acquired pneumonia. This study enrolled  
949 516 patients, 362 of which were valid for the primary efficacy analysis conducted at the 7-30 day  
950 post-therapy visit. The clinical success rate was 86% (157/182) for AVELOX therapy and 89%  
951 (161/180) for the fluoroquinolone comparators.

952

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

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

<b>Clinical Success Rates By Pathogen (Pooled CAP Studies)</b>		
<b>Pathogen</b>	<b>N</b>	<b>Success Rate</b>
<i>Streptococcus pneumoniae</i>	80/85	94%
<i>Staphylococcus aureus</i>	17/20	85%
<i>Klebsiella pneumoniae</i>	11/12	92%
<i>Haemophilus influenzae</i>	56/61	92%
<i>Chlamydia pneumoniae</i>	119/128	93%
<i>Mycoplasma pneumoniae</i>	73/76	96%
<i>Moraxella catarrhalis</i>	11/12	92%

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### **Acute Bacterial Sinusitis**

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

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

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### **Uncomplicated Skin and Skin Structure Infections**

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

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**REFERENCES** 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.  
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.

Patient Information About:

**AVELOX<sup>®</sup>**

(moxifloxacin hydrochloride)

400 mg Tablets

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999 This section contains important information about AVELOX (moxifloxacin hydrochloride), and  
1000 should be read completely before you begin treatment. This section does not take the place of  
1001 discussions with your doctor or health care professional about your medical condition or your  
1002 treatment. This section does not list all benefits and risks of AVELOX. The medicine described  
1003 here can be prescribed only by a licensed health care professional. If you have any questions  
1004 about AVELOX talk with your health care professional. Only your health care professional can  
1005 determine if AVELOX is right for you.  
1006

1007 **What is AVELOX?**

1008 AVELOX is an antibiotic used to treat lung, sinus, or skin infections caused by certain germs  
1009 called bacteria. AVELOX kills many of the types of bacteria that can infect the lungs and sinuses  
1010 and has been shown in a large number of clinical trials to be safe and effective for the treatment  
1011 of bacterial infections.  
1012

1013 Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the  
1014 common cold). AVELOX, like all other antibiotics, does not kill viruses.  
1015

1016 You should contact your doctor if you think your condition is not improving while taking  
1017 AVELOX. AVELOX Tablets are red and contain 400 mg of active drug.  
1018

1019 **How and when should I take AVELOX?**

1020 AVELOX should be taken once a day for 5-14 days depending on your prescription. It should be  
1021 swallowed and may be taken with or without food. Try to take the tablet at the same time each  
1022 day.  
1023

1024 You may begin to feel better quickly; however, in order to make sure that all bacteria are killed,  
1025 you should complete the full course of medication. Do not take more than the prescribed dose of  
1026 AVELOX even if you missed a dose by mistake. You should not take a double dose.  
1027

1028 **Who should not take AVELOX?**

1029 You should not take AVELOX if you have ever had a severe allergic reaction to any of the group  
1030 of antibiotics known as “quinolones” such as ciprofloxacin or levofloxacin.  
1031

1032 You should avoid AVELOX if you have a rare condition known as congenital prolongation of  
1033 the QT interval. If you or any of your family members have this condition you should inform  
1034 your health care professional. You should avoid AVELOX if you are being treated for heart  
1035 rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone or  
1036 sotalol. Inform your health care professional if you are taking a heart rhythm drug.  
1037

1038 You should also avoid AVELOX if the amount of potassium in your blood is low. Low  
1039 potassium can sometimes be caused by medicines called diuretics such as furosemide and  
1040 hydrochlorothiazide. If you are taking a diuretic medicine you should speak with your health  
1041 care professional.

1042

1043 If you are pregnant or planning to become pregnant while taking AVELOX, talk to your doctor  
1044 before taking this medication. AVELOX is not recommended for use during pregnancy or  
1045 nursing, as the effects on the unborn child or nursing infant are unknown.

1046

1047 AVELOX is not recommended for children.

1048

### 1049 **What are the possible side effects of AVELOX?**

1050 AVELOX is generally well tolerated. The most common side effects caused by AVELOX,  
1051 which are usually mild, include nausea, diarrhea and dizziness. You should be careful about  
1052 driving or operating machinery until you are sure AVELOX is not causing dizziness. If you  
1053 notice any side effects not mentioned in this section or you have any concerns about the side  
1054 effects you are experiencing, please inform your health care professional.

1055

1056 In some people, AVELOX, as with some other antibiotics, may produce a small effect on the  
1057 heart that is seen on an electrocardiogram test. Although this has not caused any serious  
1058 problems in more than 7900 patients who have already taken the medication in clinical studies,  
1059 in theory it could result in extremely rare cases of abnormal heartbeat which may be dangerous.  
1060 Contact your health care professional if you develop heart palpitations (fast beating), or have  
1061 fainting spells.

1062

### 1063 **What about other medicines I am taking?**

1064

1065 Tell your doctor about all other prescription and non-prescription medicines or supplements you  
1066 are taking. You should avoid taking AVELOX with certain medicines used to treat an abnormal  
1067 heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

1068

1069 Some medicines also produce an effect on the electrocardiogram test, including cisapride,  
1070 erythromycin, some antidepressants and some antipsychotic drugs. These may increase the risk  
1071 of heart beat problems when taken with AVELOX.

1072 Many antacids and multivitamins may interfere with the absorption of AVELOX and may  
1073 prevent it from working properly. You should take AVELOX either 4 hours before or 8 hours  
1074 after taking these products.

1075

### 1076 **Remember**

1077 Take your dose of AVELOX once a day.

1078 Complete the course of medication even if you are feeling better.

1079 Keep this medication out of the reach of children.

1080 This information does not take the place of discussions with your doctor or health care  
1081 professional about your medical condition or your treatment.

1082

1083

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