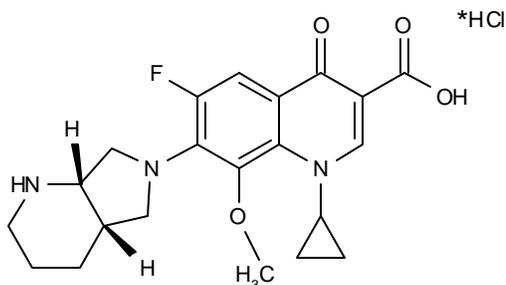


1 **AVELOX™ (moxifloxacin hydrochloride) Tablets**
2 **Final Draft Package Insert**
3 **12/10/99 (3:00 PM)**
4

5 **DESCRIPTION**
6

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



15
16 Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8-
17 position, and an S,S – configured diazabicyclononyl ring moiety at the 7-position.
18

19 AVELOX is available in 400 mg (moxifloxacin equivalent) film-coated tablets. The
20 inactive ingredients are microcrystalline cellulose, lactose monohydrate,
21 croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose,
22 titanium dioxide, polyethylene glycol and ferric oxide.
23

24 **CLINICAL PHARMACOLOGY**
25

26 **Absorption**

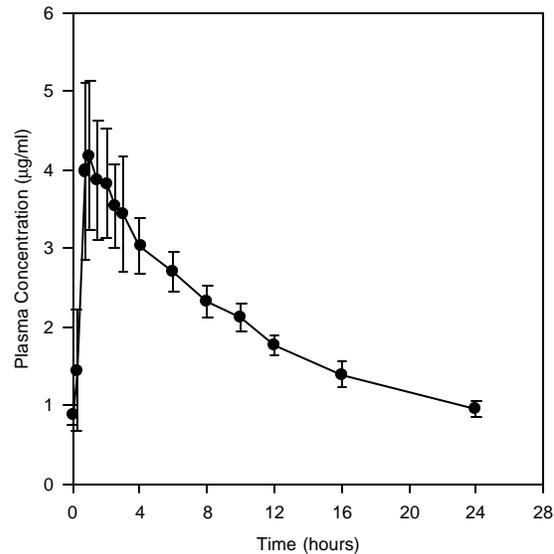
27 Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract.
28 The absolute bioavailability of moxifloxacin is approximately 90 percent. Co-
29 administration with a high fat meal (i.e., 500 calories from fat) does not affect the
30 absorption of moxifloxacin.
31

32 Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the
33 extent or rate of systemic absorption (AUC).
34

35 The mean (\pm SD) C_{max} and AUC values at steady-state with a 400 mg once daily
36 dosage regimen are $4.5 \pm 0.53 \mu\text{g/mL}$ and $48 \pm 2.7 \mu\text{g}\cdot\text{h/mL}$, respectively. C_{max} is
37 attained 1 to 3 hours after oral dosing. The mean (\pm SD) trough concentration is
38 $0.95 \pm 0.10 \mu\text{g/mL}$. Plasma concentrations increase proportionately with dose up to
39 the highest dose tested (800 mg single dose). The mean (\pm SD) elimination half-life

40 from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days
41 with a 400 mg once daily regimen. The figure below illustrates the time course of
42 plasma concentrations of moxifloxacin following a 400 mg dose administered at
43 steady-state.

**Steady-State Plasma Concentrations of Moxifloxacin
Obtained With Once Daily Dosing of 400 mg (mean;SD)
(n=10)**



44 **Distribution**

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

54
55
56
57

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

| Tissue or Fluid | N | Plasma Concentration (mg/mL) | Tissue or Fluid Concentration (mg/mL or mg/g) | Tissue: Plasma Ratio |
|-------------------------|---|------------------------------|---|----------------------|
| Respiratory | | | | |
| 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 |
| Sinus | | | | |
| Maxillary Sinus Mucosa | 4 | 3.7 ± 1.1 [†] | 7.6 ± 1.7 | 2.0 ± 0.3 |
| Anterior Ethmoid Mucosa | 3 | 3.7 ± 1.1 [†] | 8.8 ± 4.3 | 2.2 ± 0.6 |
| Nasal Polyps | 4 | 3.7 ± 1.1 [†] | 9.8 ± 4.5 | 2.6 ± 0.6 |

58 [§] all moxifloxacin concentrations were measured after a single 400 mg dose, except
59 the sinus concentrations which were measured after 5 days of dosing.

60 [†] N = 5

61

62 **Metabolism**

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

71

72 **Excretion**

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

78

79 **Special Populations**

80 **Geriatric**

81 In 16 healthy elderly male and female volunteers (66-81 years of age) given a single
82 200 mg dose of moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was
83 not statistically different between young and elderly males and elimination half-life
84 was unchanged. No dosage adjustment is necessary based on age.

85

86 Whether pharmacokinetic differences exist between young and elderly females is
87 unknown. The pharmacokinetics of moxifloxacin with repeated 400 mg
88 administration in elderly subjects has not been studied.

89 **Pediatric**

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

91 **Gender**

92 Following a single 200 mg dose of moxifloxacin to 16 healthy elderly subjects, the
93 mean AUC and C_{max} were 29% and 24% higher, respectively, in healthy elderly
94 females compared to healthy elderly males. There are no significant differences in
95 moxifloxacin pharmacokinetics between elderly male and female subjects when
96 differences in body weight are taken into consideration.

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

101 **Race**

102 Steady state moxifloxacin pharmacokinetics in male Japanese subjects were
103 similar to those determined in Caucasians, with a mean C_{max} of 4.1 $\mu\text{g/mL}$, an
104 AUC_{24} of 47 $\mu\text{g}\cdot\text{h/mL}$, and an elimination half-life of 14 hours.

105 **Renal Insufficiency**

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

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

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

122 **Hepatic Insufficiency**

123 In a single 400 mg dose study of 6 patients with mild, (Child Pugh Class A) and two
124 patients with moderate cirrhosis (Child Pugh Class B), moxifloxacin systemic

133 exposure (AUC and peak concentration (C_{max})) was reduced by approximately 23%
134 and 16%, respectively. The mean AUC of the sulfate conjugate (M1) increased by
135 4.4-fold and ranged up to 7-fold, while the mean C_{max} increased by 3.4-fold and
136 ranged up to 5.5-fold. The mean C_{max} of the glucuronide conjugate (M2) increased
137 by 1.6-fold and ranged up to 3.4-fold. The clinical significance of increased
138 exposure to the sulfate and glucuronide conjugates has not been studied. No
139 dosage adjustment is recommended for mild hepatic insufficiency (Child Pugh
140 Class A). The pharmacokinetics of moxifloxacin with moderate and severe hepatic
141 insufficiency (Child Pugh Classes B and C), however, have not been adequately
142 studied. Due to the lack of clinical data, the use of moxifloxacin is not recommended
143 with moderate and severe hepatic insufficiency. (See **DOSAGE AND**
144 **ADMINISTRATION.**)

145 **Photosensitivity Potential**

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

154 **Drug-drug interactions**

155 The potential for pharmacokinetic drug interactions between moxifloxacin and
156 theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids
157 has been evaluated. There was no clinically significant effect of moxifloxacin on
158 theophylline, warfarin, digoxin, or glyburide kinetics. Theophylline, digoxin,
159 probenecid, and ranitidine did not affect the pharmacokinetics of moxifloxacin.
160 However, as with all other quinolones, iron and antacids significantly reduced the
161 bioavailability of moxifloxacin.
162
163
164

165 **Theophylline:** No significant effect of moxifloxacin (200 mg every twelve hours for 3
166 days) on the pharmacokinetics of theophylline (400 mg every twelve hours for 3
167 days) was detected in a study involving 12 healthy volunteers. In addition,
168 theophylline was not shown to affect the pharmacokinetics of moxifloxacin. The
169 effect of co-administration of a 400 mg dose of moxifloxacin with theophylline has
170 not been studied, but it is not expected to be clinically significant based on *in vitro*
171 metabolic data showing that moxifloxacin does not inhibit the CYP1A2 isoenzyme.
172

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

178

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

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

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

195 **Antidiabetic agents:** In diabetics, glyburide (2.5 mg once daily for two weeks
196 pretreatment and for five days concurrently) mean AUC and C_{max} were 12% and 21
197 % lower, respectively, when taken with moxifloxacin (400 mg once daily for five
198 days) in comparison to placebo. Nonetheless, blood glucose levels were
199 decreased slightly in patients taking glyburide and moxifloxacin in comparison to
200 those taking glyburide alone, suggesting no interference by moxifloxacin on the
201 activity of glyburide. These interaction results are not viewed as clinically significant.

203 **Antacids:** When moxifloxacin (single 400 mg dose) was administered two hours
204 before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid
205 (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral
206 dose) to 12 healthy volunteers there was a 26%, 60% and 23% reduction in the
207 mean AUC of moxifloxacin, respectively. Moxifloxacin should be taken at least 4
208 hours before or 8 hours after antacids containing magnesium or aluminum, as well
209 as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or
210 Videx[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral
211 solution. (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND**
212 **ADMINISTRATION.**)

214 **Iron:** When moxifloxacin was administered concomitantly with iron (ferrous sulfate
215 100 mg once daily for two days), the mean AUC and C_{max} of moxifloxacin was
216 reduced by 39% and 59%, respectively. Moxifloxacin should only be taken more
217 than 4 hours before or 8 hours after iron products. (See **PRECAUTIONS, Drug**
218 **Interactions** and **DOSAGE AND ADMINISTRATION.**)

220 There is limited information available on the potential for a pharmacodynamic
221 interaction in humans between moxifloxacin and other drugs that prolong the QTc
222 interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown
223 to further increase the QTc interval when combined with high doses of intravenous
224 (IV) moxifloxacin in dogs. Therefore, moxifloxacin should not be used with Class IA

225 and Class III antiarrhythmics. (See **ANIMAL PHARMACOLOGY, WARNINGS**, and
226 **PRECAUTIONS**.)

227

228 **MICROBIOLOGY**

229 Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-
230 negative microorganisms. The bactericidal action of moxifloxacin results from
231 inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for
232 bacterial DNA replication, transcription, repair, and recombination. It appears that
233 the C8-methoxy moiety contributes to enhanced activity and lower selection of
234 resistant mutants of Gram-positive bacteria compared to the C8-H moiety.

235

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

241

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

245

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

249

250 **Aerobic Gram-positive microorganisms**

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

252 *Streptococcus pneumoniae* (penicillin-susceptible strains)

253

254 **Aerobic Gram-negative microorganisms**

255 *Haemophilus influenzae*

256 *Haemophilus parainfluenzae*

257 *Klebsiella pneumoniae*

258 *Moraxella catarrhalis*

259

260 **Other microorganisms**

261 *Chlamydia pneumoniae*

262 *Mycoplasma pneumoniae*

263

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

266

267 Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2
268 µg/mL or less against most (≥90%) strains of the following microorganisms;
269 however, the safety and effectiveness of moxifloxacin in treating clinical infections

270 due to these microorganisms have not been established in adequate and well-
271 controlled clinical trials.

272

273 **Aerobic Gram-positive microorganisms**

274 *Streptococcus pneumoniae* (penicillin-resistant strains)

275 *Streptococcus pyogenes*

276

277 **Aerobic Gram-negative microorganisms**

278 *Citrobacter freundii*

279 *Enterobacter cloacae*

280 *Escherichia coli*

281 *Klebsiella oxytoca*

282 *Legionella pneumophila*

283 *Proteus mirabilis*

284

285 **Anaerobic microorganisms**

286 *Fusobacterium* species

287 *Peptostreptococcus* species

288 *Prevotella* species

289

290 **Susceptibility Tests**

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

298

299 For testing Enterobacteriaceae and *Staphylococcus* species:

300

| 301 <u>MIC (mg/mL)</u> | 301 <u>Interpretation</u> |
|-------------------------------|----------------------------------|
| 302 ≤ 2.0 | 302 Susceptible (S) |
| 303 4.0 | 303 Intermediate (I) |
| 304 ≥ 8.0 | 304 Resistant (R) |

305

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

307

| 308 <u>MIC (mg/mL)</u> | 308 <u>Interpretation</u> |
|-------------------------------|----------------------------------|
| 309 ≤ 1.0 | 309 Susceptible (S) |

310

311 ^a This interpretive standard is applicable only to broth microdilution susceptibility
312 tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using
313 *Haemophilus* Test Medium¹.

314

315 The current absence of data on resistant strains precludes defining any results other
316 than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible “
317 category should be submitted to a reference laboratory for further testing.
318

319 For testing *Streptococcus pneumoniae*^b:
320

| <u>MIC (mg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤ 1.0 | Susceptible (S) |
| 2.0 | Intermediate (I) |
| ≥ 4.0 | Resistant (R) |

325
326 ^b This interpretive standard is applicable only to broth microdilution susceptibility
327 tests using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.
328

329 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the
330 antimicrobial compound in the blood reaches the concentrations usually achievable.
331 A report of “Intermediate” indicates that the result should be considered equivocal,
332 and, if the microorganism is not fully susceptible to alternative, clinically feasible
333 drugs, the test should be repeated. This category implies possible clinical
334 applicability in body sites where the drug is physiologically concentrated or in
335 situations where a high dosage of drug can be used. This category also provides a
336 buffer zone which prevents small uncontrolled technical factors from causing major
337 discrepancies in interpretation. A report of “Resistant” indicates that the pathogen
338 is not likely to be inhibited if the antimicrobial compound in the blood reaches the
339 concentrations usually achievable; other therapy should be selected.
340

341 Standardized susceptibility test procedures require the use of laboratory control
342 microorganisms to control the technical aspects of the laboratory procedures.
343 Standard moxifloxacin powder should provide the following MIC values:
344

| <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 |

351
352 ^c This quality control range is applicable to only *H. influenzae* ATCC 49247 tested
353 by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)¹.
354

355 ^d This quality control range is applicable to only *S. pneumoniae* ATCC 49619
356 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth
357 with 2 - 5% lysed horse blood.
358

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

365
366 Reports from the laboratory providing results of the standard single-disk
367 susceptibility test with a 5-µg moxifloxacin disk should be interpreted according to
368 the following criteria:

369
370 The following zone diameter interpretive criteria should be used for testing
371 Enterobacteriaceae and *Staphylococcus* species:

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

372
373
374
375
376
377
378 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^e:

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

379
380
381
382
383 ^e This zone diameter standard is applicable only to tests with *Haemophilus*
384 *influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium
385 (HTM)².

386
387 The current absence of data on resistant strains precludes defining any results other
388 than “Susceptible”. Strains yielding zone diameter results suggestive of a
389 “nonsusceptible” category should be submitted to a reference laboratory for further
390 testing.

391
392 For testing *Streptococcus pneumoniae*^f:

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

393
394
395
396
397
398
399 ^f These interpretive standards are applicable only to disk diffusion tests using
400 Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

401

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

405
406 As with standardized dilution techniques, diffusion methods require the use of
407 laboratory control microorganisms that are used to control the technical aspects of
408 the laboratory procedures. For the diffusion technique, the 5- μ g moxifloxacin disk
409 should provide the following zone diameters in these laboratory test quality control
410 strains:

| 411 <u>Microorganism</u> | | 412 <u>Zone Diameter (mm)</u> |
|-------------------------------------|-------------------------|-------------------------------|
| 413 <i>Escherichia coli</i> | ATCC 25922 | 28 - 35 |
| 414 <i>Haemophilus influenzae</i> | ATCC 49274 ^g | 31 - 39 |
| 415 <i>Staphylococcus aureus</i> | ATCC 25923 | 28 - 35 |
| 416 <i>Streptococcus pneumoniae</i> | ATCC 49619 ^h | 25 - 31 |

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

420
421 ^h These quality control limits are applicable only to tests conducted with *S.*
422 *pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar
423 supplemented with 5% defibrinated sheep blood.
424

425 **INDICATIONS AND USAGE**

426 AVELOX Tablets are indicated for the treatment of adults (\geq 18 years of age) with
427 infections caused by susceptible strains of the designated microorganisms in the
428 conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for
429 specific recommendations.

430
431 **Acute Bacterial Sinusitis** caused by *Streptococcus pneumoniae*, *Haemophilus*
432 *influenzae*, or *Moraxella catarrhalis*.

433
434 **Acute Bacterial Exacerbation of Chronic Bronchitis** caused by *Streptococcus*
435 *pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella*
436 *pneumoniae*, *Staphylococcus aureus*, or *Moraxella catarrhalis*.

437
438 **Community Acquired Pneumonia** (of mild to moderate severity) caused by
439 *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*,
440 *Chlamydia pneumoniae*, or *Moraxella catarrhalis*.

441
442 Appropriate culture and susceptibility tests should be performed before treatment in
443 order to isolate and identify organisms causing infection and to determine their
444 susceptibility to moxifloxacin. Therapy with AVELOX may be initiated before results
445 of these tests are known; once results become available, appropriate therapy
446 should be continued.

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CONTRAINDICATIONS

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

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 moxifloxacin should be used with caution when given concurrently with these drugs.

The effect of moxifloxacin on patients with congenital prolongation of the QT interval has not been studied, however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. 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, therefore the recommended dose should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. In 787 patients with paired valid ECGs in Phase III clinical trials, the mean \pm SD effect of moxifloxacin 400 mg on the QTc interval was 6 ± 26 msec. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 4000 patients, however certain predisposing conditions may increase the risk for ventricular arrhythmias.

492 The oral administration of moxifloxacin caused lameness in immature dogs.
493 Histopathological examination of the weight-bearing joints of these dogs revealed
494 permanent lesions of the cartilage. Related quinolone-class drugs also produce
495 erosions of cartilage of weight-bearing joints and other signs of arthropathy in
496 immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)
497

498 Convulsions have been reported in patients receiving quinolones. Quinolones may
499 also cause central nervous system (CNS) events including: dizziness, confusion,
500 tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These
501 reactions may occur following the first dose. If these reactions occur in patients
502 receiving moxifloxacin, the drug should be discontinued and appropriate measures
503 instituted. As with all quinolones, moxifloxacin should be used with caution in
504 patients with known or suspected CNS disorders (e.g. severe cerebral
505 arteriosclerosis, epilepsy) or in the presence of other risk factors that may
506 predispose to seizures or lower the seizure threshold. (See **PRECAUTIONS:**
507 **General, Information for Patients, and ADVERSE REACTIONS**.)
508

509 Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some
510 following the first dose, have been reported in patients receiving quinolone therapy.
511 Some reactions were accompanied by cardiovascular collapse, loss of
512 consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching.
513 Serious anaphylactic reactions require immediate emergency treatment with
514 epinephrine. Moxifloxacin should be discontinued at the first appearance of a skin
515 rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway
516 management, including intubation, may be administered as indicated.
517

518 Severe and sometimes fatal events, some due to hypersensitivity, and some of
519 uncertain etiology, have been reported in patients receiving therapy with all
520 antibiotics. These events may be severe and generally occur following the
521 administration of multiple doses. Clinical manifestations may include one or more of
522 the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.
523

524 **Pseudomembranous colitis has been reported with nearly all antibacterial**
525 **agents and may range in severity from mild to life-threatening. Therefore, it**
526 **is important to consider this diagnosis in patients who present with diarrhea**
527 **subsequent to the administration of antibacterial agents.**
528

529 Treatment with antibacterial agents alters the normal flora of the colon and may
530 permit overgrowth of clostridia. Studies indicate that a toxin produced by
531 *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."
532

533 After the diagnosis of pseudomembranous colitis has been established, therapeutic
534 measures should be initiated. Mild cases of pseudomembranous colitis usually
535 respond to drug discontinuation alone. In moderate to severe cases, consideration
536 should be given to management with fluids and electrolytes, protein

537 supplementation, and treatment with an antibacterial drug clinically effective against
538 *C. difficile* colitis.

539
540 Although not observed in moxifloxacin clinical trials, Achilles and other tendon
541 ruptures that required surgical repair or resulted in prolonged disability have been
542 reported with quinolones. Moxifloxacin should be discontinued if the patient
543 experiences pain, inflammation, or rupture of a tendon.

544

545 **PRECAUTIONS**

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

549

550 **Information for Patients:**

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

553

554 Patients should be advised:

555

556 ◆ that moxifloxacin may produce changes in the electrocardiogram (QTc interval
557 prolongation).

558

559 ◆ that moxifloxacin should be avoided in patients receiving Class IA (e.g.
560 quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic
561 agents.

562

563 ◆ that moxifloxacin may add to the QTc prolonging effects of other drugs such as
564 cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.

565

566 ◆ to inform their physician of any personal or family history of QTc prolongation or
567 proarrhythmic conditions such as recent hypokalemia, significant bradycardia,
568 acute myocardial ischemia.

569

570 ◆ to inform their physician of any other medications when taken concurrently with
571 moxifloxacin, including over-the-counter medications.

572

573 ◆ to contact their physician if they experience palpitations or fainting spells while
574 taking moxifloxacin.

575

576 ◆ that moxifloxacin may be taken with or without meals, and to drink fluids liberally.

577

578 ◆ that moxifloxacin should be taken at least 4 hours before or 8 hours after
579 multivitamins (containing iron or zinc), antacids (containing magnesium, calcium,
580 or aluminum), sucralfate, or Videx[®] (didanosine) chewable/buffered tablets or the
581 pediatric powder for oral solution. (See **CLINICAL PHARMACOLOGY, Drug**
582 **Interactions** and **PRECAUTIONS, Drug Interactions**.)

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- ◆ that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- ◆ to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- ◆ that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- ◆ that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with moxifloxacin at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If sunburn-like reaction or skin eruptions occur, contact your physician. (See **CLINICAL PHARMACOLOGY, Photosensitivity Potential**.)
- ◆ that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions:

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

No clinically significant drug-drug interactions between theophylline, warfarin, digoxin, or glyburide have been observed with moxifloxacin. Theophylline, digoxin, probenecid, and ranitidine have been shown not to alter the pharmacokinetics of moxifloxacin. (See **CLINICAL PHARMACOLOGY**.)

Warfarin: No significant effect of moxifloxacin on R- and S- warfarin was detected in a clinical study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in the presence of moxifloxacin. However, since some quinolones have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population, the prothrombin time or other suitable

628 coagulation test should be closely monitored if a quinolone antimicrobial is
629 administered concomitantly with warfarin or its derivatives.

630

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

636

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

641

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

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

645

646 Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA
647 1537) used in the Ames *Salmonella* reversion assay. As with other quinolones, the
648 positive response observed with moxifloxacin in strain TA 102 using the same
649 assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic
650 in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was
651 obtained in the same assay when v79 cells were used. Moxifloxacin was
652 clastogenic in the v79 chromosome aberration assay, but it did not induce
653 unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of
654 genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

655

656 Moxifloxacin had no effect on fertility in male and female rats at oral doses as high
657 as 500 mg/kg/day, approximately 12 times the maximum recommended human
658 dose based on body surface area (mg/m²). At 500 mg/kg there were slight effects
659 on sperm morphology (head-tail separation) in male rats and on the estrous cycle in
660 female rats.

661

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

663 Moxifloxacin was not teratogenic when administered to pregnant rats during
664 organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the maximum
665 recommended human dose based on systemic exposure [AUC]), but decreased
666 fetal body weights and slightly delayed fetal skeletal development (indicative of
667 fetotoxicity) were observed. Intravenous administration of 20 mg/kg/day
668 (approximately equal to the maximum recommended human oral dose based upon
669 systemic exposure) to pregnant rabbits during organogenesis resulted in
670 decreased fetal body weights and delayed fetal skeletal ossification. When rib and
671 vertebral malformations were combined, there was an increased fetal and litter
672 incidence of these effects. Signs of maternal toxicity in rabbits at this dose included
673 mortality, abortions, marked reduction of food consumption, decreased water
674 intake, body weight loss and hypoactivity. There was no evidence of teratogenicity

675 when pregnant Cynomolgus monkeys were given oral doses as high as 100
676 mg/kg/day (2.5 times the maximum recommended human dose based upon
677 systemic exposure). An increased incidence of smaller fetuses was observed at
678 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats,
679 effects observed at 500 mg/kg/day included slight increases in duration of
680 pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal
681 survival. Treatment-related maternal mortality occurred during gestation at 500
682 mg/kg/day in this study.

683

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

687

688 **Nursing Mothers:** Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin
689 may also be excreted in human milk. Because of the potential for serious adverse
690 reactions in infants nursing from mothers taking moxifloxacin, a decision should be
691 made whether to discontinue nursing or to discontinue the drug, taking into account
692 the importance of the drug to the mother.

693

694 **Pediatric Use:** Safety and effectiveness in pediatric patients and adolescents less
695 than 18 years of age have not been established. Moxifloxacin causes arthropathy in
696 juvenile animals. (See **WARNINGS**.)

697

698 **Geriatric Use:** In controlled multiple-dose clinical trials, 23% of patients receiving
699 moxifloxacin were greater than or equal to 65 years of age and 9% were greater
700 than or equal to 75 years of age. The clinical trial data demonstrate that there is no
701 difference in the safety and efficacy of moxifloxacin in patients aged 65 or older
702 compared to younger adults.

703

704 **ADVERSE REACTIONS**

705 Clinical efficacy trials enrolled over 4900 moxifloxacin treated patients, of whom
706 over 4300 patients received the 400 mg dose. Most adverse events reported in
707 moxifloxacin trials were described as mild to moderate in severity and required no
708 treatment. Moxifloxacin was discontinued due to adverse reactions thought to be
709 drug-related in 3.8% of patients.

710

711 Adverse reactions, judged by investigators to be at least possibly drug-related,
712 occurring in greater than or equal to 1% of moxifloxacin treated patients were:
713 nausea (8%), diarrhea (6%), dizziness (3%), headache (2%), abdominal pain (2%),
714 vomiting (2%), taste perversion (1%), abnormal liver function test (1%), and
715 dyspepsia (1%).

716

717 Additional events, judged by investigators to be at least possibly drug-related, that
718 occurred in greater than 0.05% and less than 1% of moxifloxacin treated patients
719 were:

720

721 BODY AS A WHOLE: asthenia, moniliasis, pain, malaise, lab test abnormal (not
722 specified), allergic reaction, leg pain, pelvic pain, abdominal pain, back pain, chills,
723 infection, pain, chest pain, hand pain
724 CARDIOVASCULAR: palpitation, vasodilatation, tachycardia, hypertension,
725 peripheral edema, hypotension
726 CENTRAL NERVOUS SYSTEM: insomnia, nervousness, anxiety, confusion,
727 hallucinations, depersonalization, hypertonia, incoordination, somnolence, tremor,
728 vertigo, paresthesia
729 DIGESTIVE: dry mouth, constipation, oral moniliasis, anorexia, stomatitis, gastritis,
730 glossitis, gastrointestinal disorder, cholestatic jaundice, GGTP increased
731 HEMIC AND LYMPHATIC: prothrombin time decrease, prothrombin time increase,
732 thrombocythemia, thrombocytopenia, eosinophilia, leukopenia
733 METABOLIC AND NUTRITIONAL: amylase increased, hyperglycemia,
734 hyperlipidemia, lactic dehydrogenase increased
735 MUSCULOSKELETAL: arthralgia, myalgia
736 RESPIRATORY: asthma, dyspnea, cough increased, pneumonia, pharyngitis,
737 rhinitis, sinusitis
738 SKIN/APPENDAGES: rash, pruritus, sweating, urticaria, dry skin,
739 SPECIAL SENSES: tinnitus, amblyopia
740 UROGENITAL: vaginal moniliasis, vaginitis, cystitis, kidney function abnormal

741

742 **LABORATORY CHANGES**

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

750

751 **OVERDOSAGE**

752 In the event of acute overdosage, the stomach should be emptied and ECG
753 monitoring is recommended due to the possible prolongation of the QT interval.
754 The patient should be carefully observed and given supportive treatment. Adequate
755 hydration must be maintained. It is not known whether moxifloxacin is dialyzable.

756

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

763

764 **DOSAGE AND ADMINISTRATION**

765 The dose of AVELOX Tablets is one 400 mg tablet taken orally every 24 hours. The
766 duration of therapy depends on the type of infection as described below.

767

| 768 | Infection * | Daily Dose | Duration |
|-----|------------------------------|-------------------|-----------------|
| 769 | | | |
| 770 | Acute Bacterial Sinusitis | 400 mg | 10 days |
| 771 | | | |
| 772 | Acute Bacterial Exacerbation | 400 mg | 5 days |
| 773 | of Chronic Bronchitis | | |
| 774 | | | |
| 775 | Community Acquired Pneumonia | 400 mg | 10 days |
| 776 | | | |

777 * due to the designated pathogens (See **INDICATIONS AND USAGE.**)

778

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

785

786 **Impaired Renal Function**

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

790

791 **Impaired Hepatic Function**

792 No dosage adjustment is required in patients with mild hepatic insufficiency (Child
793 Pugh Class A). The pharmacokinetics of moxifloxacin in patients with moderate
794 and severe hepatic insufficiency (Child Pugh Classes B and C) have not been
795 adequately studied. Due to the lack of clinical data the use of moxifloxacin is not
796 recommended in patients with moderate and severe hepatic insufficiency. (See
797 **CLINICAL PHARMACOLOGY, Hepatic Insufficiency.**)

798

799 **HOW SUPPLIED**

800 AVELOX (moxifloxacin hydrochloride) Tablets are available as oblong, dull red film-
801 coated tablets containing 400 mg moxifloxacin. The tablet is coded with the word
802 "BAYER" on one side and "M400" on the reverse side.

803

| 804 | Package | NDC Code |
|-----|----------------|-----------------|
| 805 | Bottles of 30: | 0026-8581-69 |
| 806 | ABC Pack of 5: | 0026-8581-41 |

807

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

810

811 **ANIMAL PHARMACOLOGY**

812 Quinolones have been shown to cause arthropathy in immature animals. In studies
813 in juvenile dogs oral doses of moxifloxacin \geq 30 mg/kg/day (approximately 1.5 times

814 the maximum recommended human dose based upon systemic exposure) for 28
815 days resulted in arthropathy. There was no evidence of arthropathy in mature
816 monkeys and rats at oral doses up to 135 and 500 mg/kg, respectively.

817
818 Unlike some other members of the quinolone class, crystalluria was not observed in
819 6 month repeat dose studies in rats and monkeys with moxifloxacin.

820
821 Ocular toxicity was not observed in 6 month repeat dose studies in rats and
822 monkeys. In beagle dogs, electroretinographic (ERG) changes were observed in a
823 2 week study at doses of 60 and 90 mg/kg. Histopathological changes were
824 observed in the retina from one of four dogs at 90 mg/kg, a dose associated with
825 mortality in this study.

826
827 Some quinolones have been reported to have proconvulsant activity that is
828 exacerbated with concomitant use of non-steroidal anti-inflammatory drugs
829 (NSAIDs). Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in
830 acute toxicity or potential for CNS toxicity (e.g. seizures) in mice when used in
831 combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen.

832
833 In animal studies, at plasma concentrations about five times the human therapeutic
834 level, a QT-prolonging effect of moxifloxacin was found. Electrophysiological *in vitro*
835 studies suggested an inhibition of the rapid activating component of the delayed
836 rectifier potassium current (I_{Kr}) as an underlying mechanism. In dogs, the combined
837 infusion of sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a
838 higher degree of QTc prolongation than that induced by the same dose (30mg/kg)
839 of moxifloxacin alone.

840

841 **CLINICAL STUDIES**

842

843 **Acute Bacterial Exacerbation of Chronic Bronchitis**

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

851

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

854

| 855 <u>PATHOGEN</u> | <u>AVELOX</u> | <u>Clarithromycin</u> |
|---------------------------------------|---------------|-----------------------|
| 856 | | |
| 857 <i>Streptococcus pneumoniae</i> | 100% (16/16) | 87% (20/23) |
| 858 <i>Haemophilus influenzae</i> | 89% (33/37) | 88% (36/41) |
| 859 <i>Haemophilus parainfluenzae</i> | 100% (16/16) | 100% (14/14) |
| 860 <i>Moraxella catarrhalis</i> | 85% (29/34) | 100% (24/24) |

| | | | |
|-----|------------------------------|-------------|-------------|
| 861 | <i>Staphylococcus aureus</i> | 94% (15/16) | 75% (6/8) |
| 862 | <i>Klebsiella pneumoniae</i> | 90% (18/20) | 91% (10/11) |

863

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

868

869 **Community Acquired Pneumonia**

870 A large, randomized, double-blind, controlled clinical trial was conducted in the US
871 to compare the efficacy of AVELOX Tablets (400 mg once daily) to that of high-
872 dose clarithromycin (500 mg twice daily) in the treatment of patients with clinically
873 and radiologically documented community acquired pneumonia. This study enrolled
874 474 patients (382 of which were valid for the primary efficacy analysis conducted at
875 the 14 - 35 day follow-up visit). Clinical success for clinically evaluable patients was
876 95% (184/194) for AVELOX and 95% (178/188) for high dose clarithromycin.

877

878 In addition to the trial described above, a noncomparative trial of AVELOX (400 mg
879 once daily for ten days) was also conducted in the US in patients with community
880 acquired pneumonia. The combined moxifloxacin clinical success rates by
881 pathogen for the two studies were as follows:

882

| 883 <u>PATHOGEN</u> | <u>14 - 35 DAY FOLLOW-UP</u> |
|-------------------------------------|------------------------------|
| 885 <i>Streptococcus pneumoniae</i> | 97% (30/31) |
| 886 <i>Haemophilus influenzae</i> | 92% (33/36) |
| 887 <i>Mycoplasma pneumoniae</i> | 96% (51/53) |
| 888 <i>Chlamydia pneumoniae</i> | 93% (106/114) |
| 889 <i>Moraxella catarrhalis</i> | 91% (10/11) |

890

891 The microbiological eradication rates (eradication plus presumed eradication) in
892 AVELOX treated patients were *Streptococcus pneumoniae* 97%, *Haemophilus*
893 *influenzae* 92%, and *Moraxella catarrhalis* 91%.

894

895 **Acute Bacterial Sinusitis**

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

902

903 An additional non-comparative study was conducted to gather bacteriological data
904 and to evaluate microbiological eradication in adult patients treated with AVELOX
905 400 mg once daily for seven days. All patients (n = 336) underwent antral puncture
906 in this study. Clinical success rates and eradication/presumed eradication rates at
907 the 21 to 37 day follow-up visit were 97% (29 out of 30) for *Streptococcus*

908 *pneumoniae*, 83% (15 out of 18) for *Moraxella catarrhalis*, and 80% (24 out of 30)
909 for *Haemophilus influenzae*.

910

911 **REFERENCES** 1. National Committee for Clinical Laboratory Standards, Methods
912 for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-
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915 2. National Committee for Clinical Laboratory Standards, Performance Standards
916 for Antimicrobial Disk Susceptibility Tests-Sixth Edition. Approved Standard
917 NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.

918

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929

930

Patient Information About:

AVELOX™

931

(moxifloxacin hydrochloride)

932

400 mg Tablets

933

934 This section contains important information about AVELOX (moxifloxacin
935 hydrochloride), and should be read completely before you begin treatment. This
936 section does not take the place of discussions with your doctor or health care
937 professional about your medical condition or your treatment. This section does not
938 list all benefits and risks of AVELOX. The medicine described here can be
939 prescribed only by a licensed health care professional. If you have any questions
940 about AVELOX talk with your health care professional. Only your health care
941 professional can determine if AVELOX is right for you.

942

943 **What is AVELOX?**

944

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

949

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

952

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

955

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

957

958 AVELOX should be taken once a day for 5 or 10 days depending on your
959 prescription. It should be swallowed and may be taken with or without food. Try to
960 take the tablet at the same time each day.

961

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

966

967 **Who should not take AVELOX?**

968

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

972

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

979

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

984

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

989

990 AVELOX is not recommended for children.

991

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

993

994 AVELOX is generally well tolerated. The most common side effects caused by
995 AVELOX, which are usually mild, include nausea, vomiting, stomach pain, diarrhea,
996 dizziness and headache. You should be careful about driving or operating
997 machinery until you are sure AVELOX is not causing dizziness. If you notice any

998 side effects not mentioned in this section or you have any concerns about the side
999 effects you are experiencing, please inform your health care professional.

1000

1001 In some people, AVELOX, as with some other antibiotics, may produce a small
1002 effect on the heart that is seen on an electrocardiogram test. Although this has not
1003 caused any serious problems in more than 4000 patients who have already taken
1004 the medication, in theory it could result in extremely rare cases of abnormal
1005 heartbeat which may be dangerous. Contact your health care professional if you
1006 develop heart palpitations (fast beating), or have fainting spells.

1007

1008 **Which medicines should not be used with AVELOX?**

1009

1010 You should avoid taking AVELOX with certain medicines used to treat an abnormal
1011 heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

1012

1013 Some medicines also produce an effect on the electrocardiogram test, including
1014 cisapride, erythromycin, some antidepressants and some antipsychotic drugs.
1015 These may increase the risk of heart beat problems when taken with AVELOX. For
1016 this reason it is important to let your health care provider know all of the medicines
1017 that you are using.

1018

1019 Many antacids and multivitamins may interfere with the absorption of AVELOX and
1020 may prevent it from working properly. You should take AVELOX either 4 hours
1021 before or 8 hours after taking these products.

1022

1023 **Remember**

1024

1025 Take your dose of AVELOX once a day.

1026

1027 Complete the course of medication even if you are feeling better.

1028

1029 Keep this medication out of the reach of children.

1030

1031 This information does not take the place of discussions with your doctor or health
1032 care professional about your medical condition or your treatment.