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PRESCRIBING INFORMATION

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FACTIVE® (gemifloxacin mesylate) Tablets

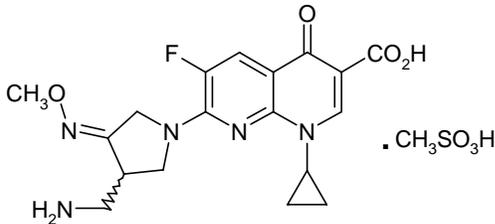
16 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
17 FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat
18 infections that are proven or strongly suspected to be caused by bacteria.

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DESCRIPTION

22 FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for
23 oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of
24 antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically,
25 gemifloxacin is (*R,S*)-7-[(4*Z*)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-
26 cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

27 The mesylate salt is a white to light brown solid with a molecular weight of
28 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 µg/mL at 37°C, pH
29 7.0). Its empirical formula is C₁₈H₂₀FN₅O₄•CH₄O₃S and its chemical structure is:



Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40 mg to 640 mg. There was minimal accumulation of gemifloxacin following multiple oral doses up to 640 mg a day for 7 days (mean accumulation <20%). Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations

42 (C_{max}) and systemic drug exposure (AUC (0-24)) were 1.61 ± 0.51 µg/mL (range 0.70-
43 2.62 µg/mL) and 9.93 ± 3.07 µg•hr/mL (range 4.71-20.1 µg•hr/mL), respectively. In
44 patients with respiratory and urinary tract infections (n=1423), similar estimates of
45 systemic drug exposure were determined using a population pharmacokinetics analysis
46 (geometric mean AUC (0-24), 8.36 µg•hr/mL; range 3.2 – 47.7 µg•hr/mL).

47 The pharmacokinetics of gemifloxacin were not significantly altered when a 320
48 mg dose was administered with a high-fat meal. Therefore FACTIVE tablets may be
49 administered without regard to meals.

50

51 **Distribution**

52 *In vitro* binding of gemifloxacin to plasma proteins in healthy subjects is approximately
53 60 to 70% and is concentration independent. After repeated doses, the *in vivo* plasma
54 protein binding in healthy elderly and young subjects ranged from 55% to 73% and was
55 unaffected by age. Renal impairment does not significantly affect the protein binding of
56 gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The
57 geometric mean for V_{dss}/F is 4.18 L/kg (range, 1.66 – 12.12 L/kg).

58 Gemifloxacin is widely distributed throughout the body after oral administration.
59 Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the
60 plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses
61 of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages,
62 epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in Table 1:
63

64

Table 1. Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean±SD)
Plasma	1.40 (0.442) µg/mL	---
Bronchoalveolar Macrophages	107 (77) µg/g	90.5 (106.3)
Epithelial Lining Fluid	2.69 (1.96) µg/mL	1.99 (1.32)
Bronchial Mucosa	9.52 (5.15) µg/g	7.21 (4.03)

65

66 **Metabolism**

67 Gemifloxacin is metabolized to a limited extent by the liver. The unchanged compound
68 is the predominant drug-related component detected in plasma (approximately 65%) up
69 to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral
70 dose); the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the
71 carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an
72 important role in gemifloxacin metabolism, and the metabolic activity of these enzymes
73 is not significantly inhibited by gemifloxacin.

74

75 **Excretion**

76 Gemifloxacin and its metabolites are excreted via dual routes of excretion. Following
77 oral administration of gemifloxacin to healthy subjects, a mean (± SD) of 61 ± 9.5% of
78 the dose was excreted in the feces and 36 ± 9.3% in the urine as unchanged drug and
79 metabolites. The mean (± SD) renal clearance following repeat doses of 320 mg was
80 approximately 11.6 ± 3.9 L/hr (range 4.6-17.6 L/hr), which indicates active secretion is
81 involved in the renal excretion of gemifloxacin. The mean (± SD) plasma elimination

82 half-life at steady state following 320 mg to healthy subjects was approximately 7 ± 2
83 hours (range 4-12 hours).

84

85 ***Special Populations***

86 **Pediatric:** The pharmacokinetics of gemifloxacin in pediatric subjects have not been
87 studied.

88

89 **Geriatric:** In adult subjects, the pharmacokinetics of gemifloxacin are not affected by
90 age.

91

92 **Gender:** There are no significant differences between gemifloxacin pharmacokinetics in
93 males and females when differences in body weight are taken into account. Population
94 pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin,
95 AUC values were approximately 10% higher in healthy female patients compared to
96 males. Males and females had mean AUC values of $7.98 \mu\text{g}\cdot\text{hr}/\text{mL}$ (range, $3.21 - 42.71$
97 $\mu\text{g}\cdot\text{hr}/\text{mL}$) and $8.80 \mu\text{g}\cdot\text{hr}/\text{mL}$ (range, $3.33 - 47.73 \mu\text{g}\cdot\text{hr}/\text{mL}$), respectively. No
98 gemifloxacin dosage adjustment based on gender is necessary.

99

100 **Hepatic Insufficiency:** The pharmacokinetics following a single 320 mg dose of
101 gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate
102 (Child-Pugh Class B) liver disease. There was a mean increase in AUC (0-inf) of 34%
103 and a mean increase in C_{max} of 25% in these patients with hepatic impairment compared
104 to healthy volunteers.

105 The pharmacokinetics of a single 320 mg dose of gemifloxacin were also studied
106 in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean
107 increase in AUC (0-inf) of 45% and a mean increase in C_{max} of 41% in these subjects
108 with hepatic impairment compared to healthy volunteers.

109 These average pharmacokinetic increases are not considered to be clinically
110 significant. There was no significant change in plasma elimination half-life in the mild,
111 moderate or severe hepatic impairment patients. No dosage adjustment is recommended
112 in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe
113 (Child-Pugh Class C) hepatic impairment. (See **DOSAGE AND ADMINISTRATION.**)

114

115 **Renal Insufficiency:** Results from population pharmacokinetic and clinical
116 pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin
117 is reduced and the plasma elimination is prolonged, leading to an average increase in
118 AUC values of approximately 70% in patients with renal insufficiency. In the
119 pharmacokinetic studies, gemifloxacin C_{max} was not significantly altered in subjects
120 with renal insufficiency. Dose adjustment in patients with creatinine clearance >40
121 mL/min is not required. Modification of the dosage is recommended for patients with
122 creatinine clearance ≤ 40 mL/min. (See **DOSAGE AND ADMINISTRATION.**)

123

124 Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from
125 plasma.

126

127

128 ***Photosensitivity Potential***

129 In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy
130 volunteers, the minimum erythematous dose (MED) was assessed following
131 administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once
132 daily, ciprofloxacin 500 mg BID, or placebo for 7 days. At 5 of the 6 wavelengths tested
133 (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically
134 different from placebo. At 365 nm (UVA region), gemifloxacin showed a
135 photosensitivity potential similar to that of ciprofloxacin 500 mg BID and the
136 photosensitivity potential for both drugs were statistically greater than that of placebo.
137 Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin
138 (0.039%). (See **ADVERSE REACTIONS**.)

139

140 ***Drug-Drug Interactions***

141 Antacids/Di- and Trivalent Cations: The systemic availability of gemifloxacin is
142 significantly reduced when an aluminum- and magnesium- containing antacid is
143 concomitantly administered (AUC decreased 85%; Cmax decreased 87%).

144 Administration of an aluminum- and magnesium- containing antacid or ferrous sulfate
145 (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the
146 systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium-
147 containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or
148 other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric
149 powder for oral solution should not be taken within 3 hours before or 2 hours after taking
150 FACTIVE tablets.

151 Calcium carbonate (1000 mg) given either 2 hr before or 2 hr after gemifloxacin
152 administration showed no notable reduction in gemifloxacin systemic availability.
153 Calcium carbonate administered simultaneously with gemifloxacin resulted in a small,
154 not clinically significant, decrease in gemifloxacin exposure [AUC (0-inf) decreased 21%
155 and Cmax decreased].

156

157 Sucralfate: When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral
158 bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69%
159 decrease in Cmax). When sucralfate (2 g) was administered 2 hours after gemifloxacin,
160 the oral bioavailability of gemifloxacin was not significantly affected; therefore
161 FACTIVE should be taken at least 2 hours before sucralfate. (See **PRECAUTIONS**.)

162

163 In Vitro Metabolism: Results of *in vitro* inhibition studies indicate that hepatic
164 cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin
165 metabolism. Therefore gemifloxacin should not cause significant *in vivo* pharmacokinetic
166 interactions with other drugs that are metabolized by CYP450 enzymes.

167

168 Theophylline: Gemifloxacin 320 mg at steady-state did not affect the repeat dose
169 pharmacokinetics of theophylline (300 to 400 mg BID to healthy male subjects).

170

171 Digoxin: Gemifloxacin 320 mg at steady-state did not affect the repeat dose
172 pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

173

174 Oral Contraceptives: The effect of an oral estrogen/progesterone contraceptive product
175 (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for
176 6 days) in healthy female subjects indicates that concomitant administration caused an
177 average reduction in gemifloxacin AUC and C_{max} of 19% and 12%. These changes are
178 not considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect
179 the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive
180 product (30 µg/150 µg once daily for 21 days to healthy female subjects).

181

182 Cimetidine: Co-administration of a single dose of 320 mg gemifloxacin with cimetidine
183 400 mg four times daily for 7 days resulted in slight average increases in gemifloxacin
184 AUC(0-inf) and C_{max} of 10% and 6%, respectively. These increases are not considered
185 clinically significant.

186

187 Omeprazole: Co-administration of a single dose of 320 mg gemifloxacin with
188 omeprazole 40 mg once daily for 4 days resulted in slight average increases in
189 gemifloxacin AUC(0-inf) and C_{max} of 10% and 11%, respectively. These increases are
190 not considered clinically significant.

191

192 Warfarin: Administration of repeated doses of gemifloxacin (320 mg once daily for 7
193 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-
194 induced anticoagulant activity (i.e., International Normalized Ratios for Prothrombin
195 Time). (See **PRECAUTIONS: Drug Interactions**.)

196

197 Probenecid: Administration of a single dose of 320 mg gemifloxacin to healthy subjects
198 who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal
199 clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in
200 gemifloxacin AUC (0-inf) and a prolongation of mean half-life by 1.6 hours. Mean
201 gemifloxacin C_{max} increased 8%.

202

203 **MICROBIOLOGY**

204 Gemifloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-
205 positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal
206 concentrations (MBCs) generally within one dilution of the minimum inhibitory
207 concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the
208 inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for
209 bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and
210 TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the
211 ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S.*
212 *pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for
213 some of these double mutants. However, the presence of double mutants was not
214 evaluated in clinical trials; therefore, the clinical significance of these *in vitro* data are
215 unknown.

216

217 The mechanism of action of quinolones, including gemifloxacin, is different from
218 that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore,
microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin

219 and other quinolones. There is no known cross-resistance between gemifloxacin and the
220 above mentioned classes of antimicrobials.

221 The main mechanism of fluoroquinolone resistance is due to mutations in DNA
222 gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep
223 mutations and efflux in a manner similar to other fluoroquinolones. The frequency of
224 spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been
225 observed between gemifloxacin and other fluoroquinolones, some microorganisms
226 resistant to other fluoroquinolones may be susceptible to gemifloxacin.

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

230

231 **Aerobic Gram-positive microorganisms**

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

233 *MDRSP, multi-drug resistant *Streptococcus pneumoniae*, includes isolates previously
234 known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant
235 to two or more of the following antibiotics: penicillin (MIC ≥ 2 $\mu\text{g/mL}$), 2nd generation
236 cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and
237 trimethoprim/sulfamethoxazole.

238

239 **Aerobic Gram-negative microorganisms**

240 *Haemophilus influenzae*

241 *Haemophilus parainfluenzae*

242 *Klebsiella pneumoniae* (many strains are only moderately susceptible)

243 *Moraxella catarrhalis*

244

245 **Other microorganisms**

246 *Chlamydia pneumoniae*

247 *Mycoplasma pneumoniae*

248

249 The following data are available, **but their clinical significance is unknown.**

250

251 Gemifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.25
252 $\mu\text{g/mL}$ or less against most ($\geq 90\%$) strains of the following microorganisms; however,
253 the safety and effectiveness of gemifloxacin in treating clinical infections due to these
254 microorganisms has not been established in adequate and well-controlled clinical trials:

255

256 **Aerobic Gram-positive microorganisms**

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

258 *Streptococcus pyogenes*

259

260 **Aerobic Gram-negative microorganisms**

261 *Acinetobacter lwoffii*

262 *Klebsiella oxytoca*

263 *Legionella pneumophila*

264 *Proteus vulgaris*

265 **Susceptibility Tests**

266 **Dilution techniques:** Quantitative methods are used to determine antimicrobial
267 minimum inhibitory concentrations (MICs). These MICs provide estimates of the
268 susceptibility of bacteria to antimicrobial compounds. The MICs should be determined
269 using a standardized procedure. Standardized procedures are based on a dilution method¹
270 (broth or agar) or equivalent with standardized inoculum concentrations and standardized
271 concentrations of gemifloxacin powder. The MICs should be interpreted according to the
272 following criteria:

273

274 For testing *Klebsiella pneumoniae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
275 ≤0.25	Susceptible (S)
276 0.5	Intermediate (I)
277 ≥1.0	Resistant (R)

278

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

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
280 ≤0.12	Susceptible (S)

281

282 ^a This interpretive standard is applicable only to broth microdilution susceptibility testing
283 with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test
284 Medium (HTM)¹.

285

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

289

290 For testing *Streptococcus pneumoniae*^b:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
291 ≤0.12	Susceptible (S)
292 0.25	Intermediate (I)
293 ≥0.5	Resistant (R)

294

295 ^b These interpretive standards are applicable only to broth microdilution susceptibility
296 tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

297

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

307

310 antimicrobial compound in the blood reaches the concentration usually achievable; other
311 therapy should be selected.

312 Standardized susceptibility test procedures require the use of laboratory control
313 microorganisms to control the technical aspects of the laboratory procedures. Standard
314 gemifloxacin powder should provide the following MIC values:

315

<u>Microorganism</u>		<u>MIC Range (µg/mL)</u>
316 <i>Enterococcus faecalis</i>	ATCC 29212	0.016-0.12
317 <i>Escherichia coli</i>	ATCC 25922	0.004-0.016
318 <i>Haemophilus influenzae</i>	ATCC 49247	0.002-0.008 ^c
319 <i>Streptococcus pneumoniae</i>	ATCC 49619	0.008-0.03 ^d

320
321
322 ^c This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a
323 broth microdilution procedure using *Haemophilus* Test Medium (HTM)¹.

324
325 ^d This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a
326 broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5%
327 lysed horse blood.

328
329 **Diffusion Techniques:** Quantitative methods that require measurement of zone
330 diameters also provide reproducible estimates of the susceptibility of bacteria to
331 antimicrobial compounds. One such standardized procedure² requires the use of
332 standardized inoculum concentrations. This procedure uses paper disks impregnated with
333 5 µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

334 Reports from the laboratory providing results of the standard single-disk
335 susceptibility test with a 5 µg gemifloxacin disk should be interpreted according to the
336 following criteria:

337
338 For testing *Klebsiella pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
339 ≥20	Susceptible (S)
340 16-19	Intermediate (I)
341 ≤15	Resistant (R)

342
343
344 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^e:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
345 ≥18	Susceptible (S)

346
347
348 ^e This interpretive standard is applicable only to disk diffusion susceptibility testing with
349 *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test
350 Medium (HTM).²

351
352 The current absence of data on resistant strains precludes defining any results
353 other than “Susceptible”. Strains yielding zone diameter results suggestive of a
354 “nonsusceptible” category should be submitted to a reference laboratory for further
355 testing.

356 For testing *Streptococcus pneumoniae*^f:

357	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
358	≥23	Susceptible (S)
359	20-22	Intermediate (I)
360	≤19	Resistant (R)

361

362 ^f These zone diameter standards apply only to tests performed using Mueller-Hinton agar
363 supplemented with 5% defibrinated sheep blood incubated in 5% CO₂.

364

365 Interpretation should be as stated above for results using dilution techniques.
366 Interpretation involves correlation of the diameter obtained in the disk test with the MIC
367 for gemifloxacin.

368

369 As with standardized dilution techniques, diffusion methods require the use of
370 laboratory control microorganisms that are used to control the technical aspects of the
371 laboratory procedures. For the diffusion technique, the 5 µg gemifloxacin disk should
372 provide the following zone diameters in these laboratory quality control strains:

373

374	<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
375	<i>Escherichia coli</i> ATCC 25922	29-36
376	<i>Haemophilus influenzae</i> ATCC 49247	30-37 ^g
377	<i>Streptococcus pneumoniae</i> ATCC 49619	28-34 ^h

378

379 ^g This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a
380 disk diffusion procedure using *Haemophilus* Test Medium (HTM)².

381

382 ^h This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a
383 disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated
384 sheep blood and incubated in 5% CO₂.

385

386 INDICATIONS AND USAGE

387 FACTIVE is indicated for the treatment of infections caused by susceptible strains of the
388 designated microorganisms in the conditions listed below. (See **DOSAGE AND**
389 **ADMINISTRATION** and **CLINICAL STUDIES**.)

390

391 **Acute bacterial exacerbation of chronic bronchitis** caused by *Streptococcus*
392 *pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella*
393 *catarrhalis*.

394

395 **Community-acquired pneumonia** (of mild to moderate severity) caused by
396 *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP])*
397 *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia*
398 *pneumoniae*, or *Klebsiella pneumoniae*.

399

400 *MDRSP, multi-drug resistant *Streptococcus pneumoniae*, includes isolates
401 previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are

402 strains resistant to two or more of the following antibiotics: penicillin (MIC \geq 2 μ g/mL),
403 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and
404 trimethoprim/sulfamethoxazole.

405

406 To reduce the development of drug-resistant bacteria and maintain the
407 effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only
408 to treat infections that are proven or strongly suspected to be caused by susceptible
409 bacteria. When culture and susceptibility information are available, they should be
410 considered in selecting or modifying antibacterial therapy. In the absence of such data,
411 local epidemiology and susceptibility patterns may contribute to the empiric selection of
412 therapy.

413

414 **CONTRAINDICATIONS**

415 FACTIVE is contraindicated in patients with a history of hypersensitivity to
416 gemifloxacin, fluoroquinolone antibiotic agents, or any of the product components.

417

418 **WARNINGS**

419 **THE SAFETY AND EFFECTIVENESS OF FACTIVE IN CHILDREN,**
420 **ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN,**
421 **AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See**
422 **PRECAUTIONS: Pediatric Use, Pregnancy and Nursing Mothers subsections.)**

423

424 **QT Effects:** Fluoroquinolones may prolong the QT interval in some patients. FACTIVE
425 should be avoided in patients with a history of prolongation of the QTc interval, patients
426 with uncorrected electrolyte disorders (hypokalemia or hypomagnesemia), and patients
427 receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol)
428 antiarrhythmic agents.

429

430 Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc
431 interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been
432 performed. FACTIVE should be used with caution when given concurrently with these
433 drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically
434 significant bradycardia or acute myocardial ischemia. **No cardiovascular morbidity or**
435 **mortality attributable to QTc prolongation occurred with FACTIVE treatment in over**
436 **8119 patients, including 707 patients concurrently receiving drugs known to prolong the**
437 **QTc interval and 7 patients with hypokalemia.**

438

439 The likelihood of QTc prolongation may increase with increasing dose of the
440 drug; therefore, the recommended dose should not be exceeded especially in patients with
441 renal or hepatic impairment where the C_{max} and AUC are slightly higher. QTc
442 prolongation may lead to an increased risk for ventricular arrhythmias including torsades
443 de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours
444 following oral administration of gemifloxacin.

445

446 **Hypersensitivity Reactions:** Serious hypersensitivity and/or anaphylactic reactions have
447 been reported in patients receiving fluoroquinolone therapy, including FACTIVE.

448

449 **Hypersensitivity reactions reported in patients receiving fluoroquinolone therapy have**
450 **occasionally been fatal.** These reactions may occur following the first dose. Some

451

448 reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure,
449 loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial
450 edema/swelling), airway obstruction (including bronchospasm, shortness of breath and
451 acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

452 FACTIVE should be discontinued immediately at the appearance of any sign of
453 an immediate type I hypersensitivity skin rash or any other manifestation of a
454 hypersensitivity reaction; the need for continued fluoroquinolone therapy should be
455 evaluated. As with other drugs, serious acute hypersensitivity reactions may require
456 treatment with epinephrine and other resuscitative measures, including oxygen,
457 intravenous fluids, antihistamines, corticosteroids, pressor amines and airway
458 management as clinically indicated. (See **PRECAUTIONS** and **ADVERSE**
459 **REACTIONS**.)

460 Other serious and sometimes fatal events, some due to hypersensitivity and some
461 due to uncertain etiology, have been reported rarely in patients receiving therapy with
462 quinolones, including FACTIVE. These events may be severe and generally occur
463 following the administration of multiple doses. **Clinical manifestations may include one**
464 **or more of the following:**

- 465 • **fever**, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis,
466 Stevens-Johnson Syndrome);
- 467 • vasculitis; arthralgia; myalgia; serum sickness;
- 468 • allergic pneumonitis;
- 469 • interstitial nephritis; acute renal insufficiency or failure;
- 470 • hepatitis; jaundice; acute hepatic necrosis or failure;
- 471 • anemia, including hemolytic and aplastic;
- 472 • thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia
473 agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

474
475 **The drug should be discontinued immediately at the first appearance of a skin**
476 **rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted**
477 **(See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).**

478
479 **Peripheral Neuropathy:** Rare cases of sensory or sensorimotor axonal polyneuropathy
480 affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias
481 and weakness have been reported in patients receiving quinolones.

482
483 **Tendon Effects:** Ruptures of the shoulder, hand, Achilles tendon or other tendons that
484 required surgical repair or resulted in prolonged disability have been reported in patients
485 receiving quinolones. Post-marketing surveillance reports indicate that this risk may be
486 increased in patients receiving concomitant corticosteroids, especially the elderly.
487 FACTIVE should be discontinued if the patient experiences pain, inflammation, or
488 rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of
489 tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after
490 therapy with quinolones.

491
492 **CNS Effects:** In clinical studies with FACTIVE, central nervous system (CNS) effects
493 have been reported infrequently. As with other fluoroquinolones, FACTIVE should be

494 used with caution in patients with CNS diseases such as epilepsy or patients predisposed
 495 to convulsions. Although not seen in FACTIVE clinical trials, convulsions, increased
 496 intracranial pressure, and toxic psychosis have been reported in patients receiving other
 497 fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety,
 498 lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely
 499 suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions
 500 occur in patients receiving FACTIVE, the drug should be discontinued and appropriate
 501 measures instituted.

502

503 ***Clostridium difficile* Associated Diarrhea:** *Clostridium difficile* associated diarrhea
 504 (CDAD) has been reported with use of nearly all antibacterial agents, including
 505 FACTIVE, and may range in severity from mild diarrhea to fatal colitis. Treatment with
 506 antibacterial agents alters the normal flora of the colon leading to overgrowth of *C.*
 507 *difficile*.

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

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

518

519 **PRECAUTIONS**

520 **General:** Prescribing FACTIVE in the absence of a proven or strongly suspected
 521 bacterial infection is unlikely to provide benefit to the patient and increases the risk of the
 522 development of drug-resistant bacteria.

523

524 **Rash:** In clinical studies, rash occurred more often with FACTIVE than with therapy
 525 with comparator agents (2.7% vs 0.6%). Increasing incidence of rash was associated
 526 with younger age (especially below 40), female gender, use of hormone replacement
 527 therapy and longer durations of therapy (see Table 2). Urticarial reactions, some of
 528 which were not classified as rash, were more common in FACTIVE patients than in
 529 comparator patients (0.6% vs 0.2%). FACTIVE should be discontinued in patients
 530 developing a rash or urticaria while on treatment. (See **ADVERSE REACTIONS** and
 531 **CLINICAL STUDIES**.)

532

533 **Table 2. Rash Incidence in FACTIVE Treated Patients from the Clinical Studies**
 534 **Population* by Gender, Age, and Duration of Therapy**

Gender & Age (yr) Category	Duration of FACTIVE Therapy			
	5 days	7 days	10 days**	14 days**
Female < 40	10/399 (2.5%)	49/407 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥ 40	30/1438 (2.1%)	34/887 (3.8%)	19/308 (6.2%)	10/126 (7.9%)
Male < 40	6/356 (1.7%)	26/453 (5.7%)	7/74 (9.5%)	3/39 (7.7%)

Male ≥ 40	10/1503 (0.7%)	26/984 (2.6%)	9/345 (2.6%)	3/116 (2.6%)
Totals	56/3696 (1.5%)	135/2732 (4.9%)	55/858 (6.4%)	23/312 (7.4%)

535 *includes patients from studies of community-acquired pneumonia, acute bacterial
 536 exacerbation of chronic bronchitis, and other indications

537 **exceeds the recommended duration of therapy (see **DOSAGE AND**
 538 **ADMINISTRATION**)

539

540 The most common form of rash associated with FACTIVE was described as
 541 maculopapular and mild to moderate in severity. Eighty percent of rashes resolved
 542 within 14 days. Approximately 10% of the rashes (0.5% of all patients) were described
 543 as of severe intensity and approximately 10% percent of those with rash were treated with
 544 systemic steroids. There were no documented cases in the clinical trials of more serious
 545 skin reactions known to be associated with significant morbidity or mortality.

546

547 Photosensitivity reactions have been reported rarely in clinical trials with
 548 FACTIVE. (See **CLINICAL PHARMACOLOGY**.) However, as with all drugs of this
 549 class, it is recommended that patients avoid unnecessary exposure to strong sunlight or
 550 artificial UV rays (e.g., sunlamps, solariums), and should be advised of the appropriate
 551 use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued
 552 if a photosensitivity reaction is suspected.

553

554 **Hepatic Effects:** Liver enzyme elevations (increased ALT and/or AST) occurred at
 555 similar rates in patients receiving FACTIVE 320 mg daily relative to comparator
 556 antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil,
 557 amoxicillin/clavulanate potassium, and ofloxacin). In patients who received
 558 gemifloxacin at doses of 480 mg per day or greater there was an increased incidence of
 559 elevations in liver enzymes. (See **ADVERSE REACTIONS**.)

560

561 There were no clinical symptoms associated with these liver enzyme elevations.
 562 The liver enzyme elevations resolved following cessation of therapy. The recommended
 563 dose of FACTIVE 320 mg daily should not be exceeded and the recommended length of
 564 therapy should not be exceeded. (See **DOSAGE AND ADMINISTRATION**.)

565

566 **Renal Effects:** Alteration of the dosage regimen is necessary for patients with
 567 impairment of renal function (creatinine clearance ≤40 mL/min). (See **DOSAGE AND**
 568 **ADMINISTRATION**.)

569

570 Adequate hydration of patients receiving FACTIVE should be maintained to
 571 prevent the formation of a highly concentrated urine.

572

573 **Information for Patients**

574 **Patients should be counseled:**

- 575 • that antibacterial drugs including FACTIVE should only be used to treat bacterial
 576 infections. They do not treat viral infections (e.g., the common cold). When
 577 FACTIVE is prescribed to treat a bacterial infection, patients should be told that
 578 although it is common to feel better early in the course of therapy, the medication
 should be taken exactly as directed. Skipping doses or not completing the full course
 of therapy may (1) decrease effectiveness of the immediate treatment and (2) increase

-
- 579 the likelihood that bacteria will develop resistance and will not be treatable by
580 FACTIVE or other antibacterial drugs in the future;
- 581 • that FACTIVE has been associated with rash and hives. Rash occurs more commonly
582 in those under 40, especially women and in women on hormone replacement therapy.
583 The incidence of rash increases with duration more than 5 days and particularly
584 longer than 7 days. Patients should discontinue FACTIVE and call their healthcare
585 provider if they develop a rash;
 - 586 • that FACTIVE may be associated with hypersensitivity reactions, including
587 anaphylactic reactions, even following a single dose; patients should immediately
588 discontinue the drug at the sign of a rash or other allergic reaction and seek medical
589 care;
 - 590 • that diarrhea is a common problem caused by antibiotics which usually ends when the
591 antibiotic is discontinued. Sometimes after starting treatment with antibiotics,
592 patients can develop watery and bloody stools (with or without stomach cramps and
593 fever) even as late as two or more months after having taken the last dose of the
594 antibiotic. If this occurs, patients should contact their physician as soon as possible;
 - 595 • that FACTIVE may cause changes in the electrocardiogram (QTc interval
596 prolongation);
 - 597 • that FACTIVE should be avoided in patients receiving Class IA (e.g., quinidine,
598 procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;
 - 599 • that FACTIVE should be used with caution in patients receiving drugs that affect the
600 QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic
601 antidepressants;
 - 602 • to inform their physician of any personal or family history of QTc prolongation or
603 proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial
604 ischemia;
 - 605 • to contact their physician if they experience palpitations or fainting spells while
606 taking FACTIVE;
 - 607 • that FACTIVE may cause dizziness; if this occurs, patients should not operate an
608 automobile or machinery or engage in activities requiring mental alertness or
609 coordination;
 - 610 • that they should discontinue FACTIVE therapy and inform their physician if they feel
611 pain, tenderness or rupture of a tendon. Patients should rest and avoid exercise until
612 the diagnosis of tendonitis or tendon rupture has been excluded. The risk of serious
613 tendon disorders is higher in those over 65 years of age, especially those on steroids;
 - 614 • that convulsions have been reported in patients receiving quinolones. Patients should
615 notify their physician before taking FACTIVE if they have a history of convulsions,
616 seizures, or epilepsy;
 - 617 • that other central nervous system problems such as tremors, restlessness,
618 lightheadedness, confusion and hallucinations may occur rarely;
 - 619 • that phototoxicity has been reported with certain quinolones. The potential for
620 FACTIVE to cause phototoxicity was low. In keeping with good clinical practice,
621 avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds). If a
622 sunburn-like reaction or skin eruption occurs, contact your physician; (See
623 **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);
-

-
- 624 • that increases of the International Normalized Ratio (INR), or prothrombin time (PT),
625 and/or clinical episodes of bleeding have been noted with concurrent administration
626 of warfarin or its derivatives, and FACTIVE. Patients should notify their physicians
627 if they are taking warfarin or its derivatives;
- 628 • to inform their physician of any other medications when taken concurrently with
629 FACTIVE, including over-the-counter medications and dietary supplements;
- 630 • that FACTIVE may be taken with or without meals;
- 631 • to drink fluids liberally;
- 632 • not to take antacids containing magnesium and/or aluminum or products containing
633 ferrous sulfate (iron), multivitamin preparations containing zinc or other metal
634 cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for
635 oral solution within 3 hours before or 2 hours after taking FACTIVE tablets;
- 636 • that FACTIVE should be taken at least 2 hours before sucralfate.

637

638 **Drug Interactions:** Administration of repeat doses of FACTIVE had no effect on the
639 repeat dose pharmacokinetics of theophylline, digoxin or an

640 ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. (See

641 **CLINICAL PHARMACOLOGY: Drug-Drug Interactions.**)

642 Concomitant administration of FACTIVE and calcium carbonate, cimetidine,
643 omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in
644 the pharmacokinetics of gemifloxacin, which were considered to be without clinical
645 significance. (See **CLINICAL PHARMACOLOGY.**)

646 Concomitant administration of FACTIVE with probenecid resulted in a 45%
647 increase in systemic exposure to gemifloxacin. (See **CLINICAL**
648 **PHARMACOLOGY.**)

649 FACTIVE had no significant effect on the anticoagulant effect of warfarin in
650 healthy subjects on stable warfarin therapy. However, post-marketing reports of
651 increases in the INR, or PT, and/or clinical episodes of bleeding in patients have been
652 noted with the use of quinolones, including FACTIVE, and warfarin, or its derivatives.
653 In addition, infectious disease and its accompanying inflammatory process, age and
654 general status of the patient are risk factors for increased anticoagulation activity.
655 Therefore, the PT, INR or other suitable coagulation test should be closely monitored if a
656 quinolone antimicrobial, including FACTIVE, is administered concomitantly with
657 warfarin or its derivatives.

658 Quinolones form chelates with alkaline earth and transition metals. The
659 absorption of oral gemifloxacin is significantly reduced by the concomitant
660 administration of an antacid containing aluminum and magnesium. Magnesium- and/or
661 aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin
662 preparations containing zinc or other metal cations, or Videx® (didanosine)
663 chewable/buffered tablets or the pediatric powder for oral solution should not be taken
664 within 3 hours before or 2 hours after FACTIVE. Sucralfate should not be taken within 2
665 hours of FACTIVE. (See **CLINICAL PHARMACOLOGY.**)

666

667 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

668 *Carcinogenesis:* Long term studies in animals to determine the carcinogenic potential of
669 gemifloxacin have not been conducted.

670

671 *Photocarcinogenesis:* Gemifloxacin did not shorten the time to development of UVR-
672 induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photocarcinogenic in
673 this model. These mice received oral gemifloxacin and concurrent irradiation with
674 simulated sunlight 5 days per week for 40 weeks followed by a 12-week treatment-free
675 observation period. The daily dose of UV radiation used in this study was approximately
676 1/3 of the minimal dose of UV radiation that would induce erythema in Caucasian
677 humans. The median time to the development of skin tumors in the hairless mice was
678 similar in the vehicle control group (36 weeks) and those given up to 100 mg/kg
679 gemifloxacin daily (39 weeks). Following repeat doses of 100 mg/kg gemifloxacin per
680 day, the mice had skin gemifloxacin concentrations of approximately 7.4 µg/g. Plasma
681 levels following this dose were approximately 1.4 µg/mL in the mice around the time of
682 irradiation. There are no data on gemifloxacin skin levels in humans, but the mouse
683 plasma gemifloxacin levels are in the expected range of human plasma C_{max} levels (0.7-
684 2.6 µg/mL, with an overall mean of about 1.6 µg/mL) following multiple 320 mg oral
685 doses.

686

687 *Mutagenesis:* Gemifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA
688 1535, TA 1537) used in an Ames *Salmonella* reversion assay. It did not induce
689 micronuclei in the bone marrow of mice following intraperitoneal doses of up to 40
690 mg/kg and it did not induce unscheduled DNA synthesis in hepatocytes from rats which
691 received oral doses of up to 1600 mg/kg. Gemifloxacin was clastogenic *in vitro* in the
692 mouse lymphoma and human lymphocyte chromosome aberration assays. It was
693 clastogenic *in vivo* in the rat micronucleus assay at oral and intravenous dose levels (≥800
694 mg/kg and ≥40 mg/kg, respectively) that produced bone marrow toxicity.
695 Fluoroquinolone clastogenicity is apparently due to inhibition of mammalian
696 topoisomerase activity which has threshold implications.

697

698 *Impairment of Fertility:* Gemifloxacin did not affect the fertility of male or female rats at
699 AUC levels following oral administration (216 and 600 mg/kg/day) that were
700 approximately 3- to 4-fold higher than the AUC levels at the clinically recommended
701 dose.

702

703 **Pregnancy: Teratogenic Effects. Pregnancy Category C.** Gemifloxacin treatment
704 during organogenesis caused fetal growth retardation in mice (oral dosing at 450
705 mg/kg/day), rats (oral dosing at 600 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day)
706 at AUC levels which were 2-, 4- and 3-fold those in women given oral doses of 320 mg.
707 In rats, this growth retardation appeared to be reversible in a pre- and postnatal
708 development study (mice and rabbits were not studied for the reversibility of this effect).
709 Treatment of pregnant rats at 8-fold clinical exposure (based upon AUC comparisons)
710 caused fetal brain and ocular malformations in the presence of maternal toxicity. The
711 overall no-effect exposure level in pregnant animals was approximately 0.8 to 3-fold
712 clinical exposure.

713

714

The safety of FACTIVE in pregnant women has not been established. FACTIVE should not be used in pregnant women unless the potential benefit to the mother

715 outweighs the risk to the fetus. There are no adequate and well-controlled studies in
716 pregnant women.

717

718 **Nursing Mothers:** Gemifloxacin is excreted in the breast milk of rats. There is no
719 information on excretion of gemifloxacin into human milk. Therefore, FACTIVE should
720 not be used in lactating women unless the potential benefit to the mother outweighs the
721 risk.

722

723 **Pediatric Use:** Safety and effectiveness in children and adolescents less than 18 years of
724 age have not been established. Fluoroquinolones, including gemifloxacin, cause
725 arthropathy and osteochondrosis in immature animals. (See **WARNINGS**.)

726

727 **Geriatric Use:** Of the total number of subjects in clinical studies of FACTIVE, 29%
728 (2314) were 65 and over, while 11% (865) were 75 and over. No overall difference in
729 effectiveness was observed between these subjects and younger subjects; the adverse
730 event rate for this group was similar to or lower than that for younger subjects with the
731 exception that the incidence of rash was lower in geriatric patients compared to patients
732 less than 40 years of age.

733

734 Elderly patients may be more susceptible to drug-associated effects on the QT
735 interval. Therefore, FACTIVE should be avoided in patients taking drugs that can result
736 in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in
737 patients with risk factors for torsades de pointes (e.g., known QT prolongation,
738 uncorrected hypokalemia).

739

740 Patients over 65 are at increased risk for developing severe tendon disorders
741 including tendon rupture when being treated with a fluoroquinolone such as FACTIVE.
742 This risk is further increased in patients receiving concomitant steroid therapy. Tendon
743 rupture usually involves the Achilles, hand or shoulder tendons and can occur during
744 therapy or up to a few months post completion of therapy. Caution should be used when
745 prescribing FACTIVE to elderly patients especially those on corticosteroids. Patients
746 should be informed of this potential side effect and advised to discontinue therapy and
747 inform their physicians if any tendon symptoms occur.

748

749 **ADVERSE REACTIONS**

750

751 In clinical studies, 8119 patients received daily oral doses of 320 mg FACTIVE. In
752 addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment
753 received single or repeat doses of gemifloxacin in clinical pharmacology studies. The
754 majority of adverse reactions experienced by patients in clinical trials were considered to
755 be of mild to moderate severity.

756

757 FACTIVE was discontinued because of an adverse event (determined by the
758 investigator to be possibly or probably related to drug) in 2.0% of patients, primarily due
759 to rash (0.8%), nausea (0.3%), diarrhea (0.3%), urticaria (0.2%) and vomiting (0.2%).
760 Comparator antibiotics were discontinued because of an adverse event at an overall
761 comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.4%), vomiting
(0.3%), rash (0.3%), abdominal pain (0.2%), and vertigo (0.2%).

762

763 The most commonly reported adverse events with a frequency of $\geq 2\%$ for patients
764 receiving 320 mg of FACTIVE versus comparator drug (beta-lactam antibiotics),

761 macrolides or other fluoroquinolones) are as follows: diarrhea 5.0% vs. 6.2%; rash 3.5%
 762 vs. 1.1%; nausea 3.7% vs. 4.5%; headache 4.2% vs. 5.2%; abdominal pain 2.2% vs.
 763 2.2%; vomiting 1.6% vs. 2.0%; and dizziness 1.7% vs. 2.6%.

764 FACTIVE appears to have a low potential for photosensitivity. In clinical trials,
 765 treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.

766
 767 **Adverse Events with a Frequency of Less than 1%**

768 Additional drug-related adverse events (possibly or probably related) in the 8119 patients,
 769 with a frequency of >0.1% to ≤1% included: abdominal pain, anorexia, constipation,
 770 dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis,
 771 genital moniliasis, genital pruritus, hyperglycemia, increased alkaline phosphatase,
 772 increased ALT, increased AST, increased creatine phosphokinase, insomnia, leukopenia,
 773 pruritus, somnolence, taste perversion, thrombocytopenia, urticaria, vaginitis, and
 774 vomiting.

775 Other adverse events reported from clinical trials which have potential clinical
 776 significance and which were considered to have a suspected relationship to the drug, that
 777 occurred in ≤0.1% of patients were: abnormal urine, abnormal vision, anemia, arthralgia,
 778 asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, facial edema, flushing,
 779 gastroenteritis, granulocytopenia, hot flashes, increased GGT, increased non-protein
 780 nitrogen, leg cramps, moniliasis, myalgia, nervousness, non-specified gastrointestinal
 781 disorder, pain, pharyngitis, pneumonia, thrombocytopenia, tremor, vertigo.

782 In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB)
 783 and community acquired pneumonia (CAP), the incidences of rash were as follows
 784 (Table 3):

785
 786 **Table 3. Incidence of Rash by Clinical Indication in Patients Treated with**
 787 **FACTIVE**
 788

	ABECB (5 days) N = 2284		CAP (5 days) N = 256		CAP (7 days) N = 643	
	n/N	%	n/N	%	n/N	%
Totals	27/2284	1.2	1/256	0.4	26/643	4.0
Females, < 40 years	NA*		1/37	2.7	8/88	9.1
Females, ≥ 40 years	16/1040	1.5	0/73	0	5/214	2.3
Males, < 40 years	NA*		0/65	0	5/101	5.0
Males, ≥ 40 years	11/1203	0.9	0/81	0	8/240	3.3

* insufficient number of patients in this category for a meaningful analysis

789
 790 (See PRECAUTIONS).
 791

792 **Laboratory Changes:** The percentages of patients who received multiple doses of
 793 FACTIVE and had a laboratory abnormality are listed below. It is not known whether
 794 these abnormalities were related to FACTIVE or an underlying condition.

795 Clinical Chemistry: increased ALT (1.7%), increased AST (1.3%), increased
 796 creatine phosphokinase (0.7%), increased alkaline phosphatase (0.4%), increased total
 797 bilirubin (0.4%), increased potassium (0.3%), decreased sodium (0.2%), increased blood

798 urea nitrogen (0.3%), decreased albumin (0.3%), increased serum creatinine (0.2%),
799 decreased calcium (0.1%), decreased total protein (0.1%), decreased potassium (0.1%),
800 increased sodium (0.1%), increased lactate dehydrogenase (<0.1%) and increased
801 calcium (<0.1%).

802 CPK elevations were noted infrequently: 0.7% in FACTIVE patients vs. 0.7% in
803 the comparator patients.

804 **Hematology:** increased platelets (1.0%), decreased neutrophils (0.5%), increased
805 neutrophils (0.5%), decreased hematocrit (0.3%), decreased hemoglobin (0.2%),
806 decreased platelets (0.2%), decreased red blood cells (0.1%), increased hematocrit
807 (0.1%), increased hemoglobin (0.1%), and increased red blood cells (0.1%).

808 In clinical studies, approximately 7% of the FACTIVE treated patients had
809 elevated ALT values immediately prior to entry into the study. Of these patients,
810 approximately 15% showed a further elevation of their ALT at the on-therapy visit and
811 9% showed a further elevation at the end of therapy visit. None of these patients
812 demonstrated evidence of hepatocellular jaundice. For the pooled comparators,
813 approximately 6% of patients had elevated ALT values immediately prior to entry into
814 the study. Of these patients, approximately 7% showed a further elevation of their ALT
815 at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

816 In a clinical trial where 638 patients received either a single 640 mg dose of
817 gemifloxacin or 250 mg BID of ciprofloxacin for 3 days, there was an increased
818 incidence of ALT elevations in the gemifloxacin arm (3.9%) vs. the comparator arm
819 (1.0%). In this study, two patients experienced ALT elevations of 8 to 10 times the upper
820 limit of normal. These elevations were asymptomatic and reversible.

821

822 **Post-Marketing Adverse Reactions:** The majority of the post-marketing adverse events
823 reported were cutaneous and most of these were rash. Some of these cutaneous adverse
824 events were considered serious. The majority of rashes occurred in women and in
825 patients under 40 years of age.

826

827 The following are additional adverse reactions reported during the post-marketing use of
828 FACTIVE. Since these reactions are reported voluntarily from a population of uncertain
829 size, it is impossible to reliably estimate their frequency or establish a causal relationship
830 to FACTIVE exposure:

- 831 • anaphylactic reaction, erythema multiforme, skin exfoliation, facial swelling;
- 832 • hemorrhage, increased international normalized ratio (INR), retinal hemorrhage;
- 833 • peripheral edema;
- 834 • renal failure;
- 835 • prolonged QT, supraventricular tachycardia, syncope, transient ischemic attack;
- 836 • antibiotic-associated colitis.

837

838 **OVERDOSAGE**

839 Any signs or symptoms of overdosage should be treated symptomatically. No specific
840 antidote is known. In the event of acute oral overdosage, the stomach should be emptied
841 by inducing vomiting or by gastric lavage; the patient should be carefully observed and
842 treated symptomatically with appropriate hydration maintained. Hemodialysis removes
843 approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

844 Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320
845 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80
846 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400
847 mg/kg) of gemifloxacin to rodents included ataxia, lethargy, piloerection, tremor, and
848 clonic convulsions.

849

850 **DOSAGE AND ADMINISTRATION**

851 FACTIVE can be taken with or without food and should be swallowed whole with a
852 liberal amount of liquid. The recommended dose of FACTIVE is 320 mg daily,
853 according to the following table (Table 4).

854

855 **Table 4. Recommended Dosage Regimen of FACTIVE**

856 The clinical decision regarding the use of a 5 day or 7 day regimen should be guided by
857 results of the initial sputum culture.

858

INDICATION	DOSE/DURATION
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily for 5 days
Community-acquired pneumonia (of mild to moderate severity)	
<i>due to known or suspected S. pneumoniae, H. influenzae, M. pneumoniae, or C. pneumoniae infection</i>	One 320 mg tablet daily for 5 days
<i>due to known or suspected MDRSP*, K. pneumoniae, or M. catarrhalis infection</i>	One 320 mg tablet daily for 7 days

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

859

860 The recommended dose and duration of FACTIVE should not be exceeded (see Table 2).

861

862 **Use in Renally Impaired Patients:** Dose adjustment in patients with creatinine clearance
863 >40 mL/min is not required. Modification of the dosage is recommended for patients
864 with creatinine clearance ≤40 mL/min. Table 5 provides dosage guidelines for use in
865 patients with renal impairment:

866

867 **Table 5. Recommended Doses for Patients with Renal Impairment**

Creatinine Clearance (mL/min)	Dose
>40	See Usual Dosage
≤40	160 mg every 24 hours

868

869 Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis
870 (CAPD) should receive 160 mg every 24 hours.

871

872 When only the serum creatinine concentration is known, the following formula
873 may be used to estimate creatinine clearance.

874

875 Men: Creatinine Clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

876

877 Women: 0.85 x the value calculated for men

878

879 **Use in Hepatically Impaired Patients:** No dosage adjustment is recommended in
880 patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe
881 (Child-Pugh Class C) hepatic impairment.

882

883 **Use in Elderly:** No dosage adjustment is recommended.

884

885 HOW SUPPLIED

886 FACTIVE (gemifloxacin mesylate) is available as white to off-white, oval, film-coated
887 tablets with breaklines and GE 320 debossed on both faces. Each tablet contains
888 gemifloxacin mesylate equivalent to 320 mg of gemifloxacin.

889

890 320 mg Unit of Use (CR*) 5's NDC 67707-320-05

891 320 mg Unit of Use (CR*) 7's NDC 67707-320-07

892 *Child Resistant

893

894 Storage

895 Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled
896 Room Temperature]. Protect from light.

897

898 ANIMAL PHARMACOLOGY

899 Quinolones have been shown to cause arthropathy in immature animals. Degeneration of
900 articular cartilage occurred in juvenile dogs given at least 192 mg/kg/day gemifloxacin in
901

902 a 28-day study (producing about 6 times the systemic exposure at the clinical dose), but
903 not in mature dogs. There was no damage to the articular surfaces of joints in immature
904 rats given repeated doses of up to 800 mg/kg/day.

905 Some quinolones have been reported to have proconvulsant properties that are
906 potentiated by the concomitant administration of non-steroidal anti-inflammatory drugs
907 (NSAIDs). Gemifloxacin alone had effects in tests of behavior or CNS interaction
908 typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the
909 active metabolite of the NSAID, fenbufen, followed by 80 mg/kg gemifloxacin.

910 Dogs given 192 mg/kg/day (about 6 times the systemic exposure at the clinical
911 dose) for 28 days, or 24 mg/kg/day (approximately equivalent to the systemic exposure at
912 the clinical dose) for 13 weeks showed reversible increases in plasma ALT activities and
913 local periportal liver changes associated with blockage of small bile ducts by crystals
914 containing gemifloxacin.

915 Quinolones have been associated with prolongation of the electrocardiographic
916 QT interval in dogs. Gemifloxacin produced no effect on the QT interval in dogs dosed
917 orally to provide about 4 times human therapeutic plasma concentrations at C_{max}, and
918 transient prolongation after intravenous administration at more than 4 times human
919 plasma levels at C_{max}. Gemifloxacin exhibited weak activity in the cardiac I_{Kr} (hERG)
920 channel inhibition assay, having an IC₅₀ of approximately 270 μM.

921 Gemifloxacin, like many other quinolones, tends to crystallize at the alkaline pH
922 of rodent urine, resulting in a nephropathy in rats that is reversible on drug withdrawal
923 (oral no-effect dose 24 mg/kg/day).

924 Gemifloxacin was weakly phototoxic to hairless mice given a single 200 mg/kg
925 oral dose and exposed to UVA radiation. However, no evidence of phototoxicity was
926 observed at 100 mg/kg/day dosed orally for 13 weeks in a standard hairless mouse model,
927 using simulated sunlight.

928

929 **CLINICAL STUDIES**

930 **Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)**

931 FACTIVE (320 mg once daily for 5 days) was evaluated for the treatment of acute
932 bacterial exacerbation of chronic bronchitis in three pivotal double-blind, randomized,
933 actively-controlled clinical trials (studies 068, 070, and 212). The primary efficacy
934 parameter in these studies was the clinical response at follow-up (day 13 to 24). The
935 results of the clinical response at follow-up for the principal ABECB studies demonstrate
936 that FACTIVE 320 mg PO once daily for 5 days was at least as good as the comparators
937 given for 7 days. The results are shown in Table 6 below.

938

939 **Table 6. Clinical Response at Follow-Up (Test of Cure): Pivotal ABECB Studies**

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
Study 068		
FACTIVE 320 mg x 5 days	86.0 (239/278)	1.2 (-4.7, 7.0)
Clarithromycin 500 mg BID x 7 days	84.8 (240/283)	
Study 070		
FACTIVE 320 mg x 5 days	93.6 (247/264)	0.4 (-3.9, 4.6)

Amoxicillin/clavulanate 500 mg/125 mg TID x 7 days	93.2 (248/266)	
Study 212		
FACTIVE 320 mg x 5 days	88.2 (134/152)	3.1 (-4.7, 10.7)
Levofloxacin 500 mg x 7 days	85.1 (126/148)	

940

941 **Community Acquired Pneumonia (CAP)**

942 **5 Day Treatment Regimen**

943 To evaluate the safety and efficacy of a 5-day course of FACTIVE, 510 outpatient and
 944 hospitalized adults with clinically and radiologically determined mild to moderate
 945 community-acquired pneumonia were clinically evaluated in a double-blind, randomized,
 946 prospective, multicenter study comparing FACTIVE 320 mg for five days to
 947 gemifloxacin 320 mg for seven days (Study OP-634-001).

948

949 Clinical success rates in the clinically evaluable population were 95.0% in the 5
 950 day group and 92.1% in the 7 day group.

951

952 **Table 7. Clinical Response at Follow-Up (Test of Cure): Study OP-634-001**

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
Study OP-634-001		
FACTIVE 320 mg x 5 days	95.0 (230/242)	3.0 (-1.5, 7.4)
FACTIVE 320 mg x 7 days	92.1 (209/227)	

953

954 The microbiological efficacy of the 5-day regimen was documented for pathogens
 955 listed in Table 8 below.

956

957 **Table 8. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in**
 958 **Study OP-634-001**

959

Pathogen	5-day		7-day	
	n/N	%	n/N	%
<i>Streptococcus pneumoniae</i>	26/26	100	34/40	85.0
<i>Mycoplasma pneumoniae</i>	22/25	88.0	19/20	95.0
<i>Haemophilus influenzae</i>	21/22	95.5	18/18	100
<i>Chlamydia pneumoniae</i>	17/18	94.4	30/31	96.8

960

961 **7-Day Treatment Regimen**

962 Previous clinical studies evaluated the efficacy of FACTIVE in a 7-day treatment of CAP
 963 in adults. This clinical program consisted of three double-blind, randomized, actively-
 964 controlled clinical studies (studies 011, 012, and 049) and one open-label, actively-
 965 controlled study (study 185). In addition, two uncontrolled studies (studies 061 and 287)
 966 were conducted. Three of the studies, controlled study 011 and the uncontrolled studies,

967 had a fixed 7-day duration of treatment for FACTIVE. Controlled study 011 compared a
 968 7-day course of FACTIVE with a 10-day treatment course of amoxicillin/clavulanate
 969 (1g/125 mg TID) and clinical success rates were similar between treatment arms. The
 970 results of comparative studies 049, 185, and 012 were supportive although treatment
 971 duration could have been 7 to 14 days. The results of the clinical studies with a fixed
 972 7-day duration of gemifloxacin are shown in Table 9:

973
 974 **Table 9. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7-**
 975 **day Duration of Treatment**

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
Study 011		
FACTIVE 320 mg x 7 days	88.7 (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 1 g/125 mg TID x 10 days	87.6 (99/113)	
Study 061		
FACTIVE 320 mg x 7 days	91.7 (154/168)	(86.1, 95.2)
Study 287		
FACTIVE 320 mg x 7 days	89.8 (132/147)	(84.9, 94.7)

976 *For uncontrolled studies, the 95% CI around the success rate is shown

977

978 The combined bacterial eradication rates for patients treated with a fixed 7-day
 979 treatment regimen of FACTIVE are shown in Table 10:

980

981 **Table 10. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in**
 982 **Studies with a Fixed 7-day Duration of Treatment**

Pathogen	n/N	%
<i>S. pneumoniae</i>	102/117	87.2
<i>M. pneumoniae</i>	40/42	95.2
<i>H. influenzae</i>	48/53	90.6
<i>C. pneumoniae</i>	43/45	95.6
<i>K. pneumoniae</i>	18/20	90.0
<i>M. catarrhalis</i>	11/12	91.7

983

984 **7-day Treatment Regimen of Community-Acquired Pneumonia Due to Multi-Drug**
 985 **Resistant *Streptococcus pneumoniae* (MDRSP)**

986 FACTIVE was also effective in the treatment of CAP due to multi-drug resistant
 987 *Streptococcus pneumoniae* (MDRSP*). Of 35 patients with MDRSP treated for 7 days,
 988 29 (82.9%) achieved clinical and bacteriological success at follow-up. The clinical and
 989 bacteriological success for the 35 patients with MDRSP isolates are shown in Table 11.

990

991 *MDRSP: multi-drug resistant *Streptococcus pneumoniae*, includes isolates
 992 previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are
 993 strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 $\mu\text{g/mL}$),
 994 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and
 995 trimethoprim/sulfamethoxazole.
 996

997 **Table 11. Clinical and Bacteriological Success for 35 Patients Treated with**
 998 **FACTIVE in CAP Studies with a 7-day Duration of Treatment for MDRSP**

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N ^a	%	n/N ^b	%
Penicillin-resistant	15/16	93.8	15/16	93.8
2 nd generation cephalosporin-resistant	20/22	90.9	20/22	90.9
Macrolide-resistant ^c	24/28	85.7	23/28	82.1
Trimethoprim/sulfamethoxazole-resistant	23/26	88.5	23/26	88.5
Tetracycline-resistant	21/27	77.8	20/27	74.1

999

1000 ^an = the number of patients successfully treated; N = number of patients with MDRSP

1001 ^bn = the number of bacteriological isolates successfully treated; N = number of isolates
 1002 studied

1003 ^cMacrolide antibiotics tested include clarithromycin and erythromycin
 1004

1005 Not all isolates were resistant to all antimicrobial classes tested. Success and
 1006 eradication rates are summarized in the Table 10 below.
 1007

1008 **Table 12. Resistant *Streptococcus pneumoniae* Clinical Success and Bacteriological**
 1009 **Eradication Rates**
 1010

<i>S. pneumoniae</i> with MDRSP	Clinical Cure Rate		Bacteriological Eradication Rate	
	n/N	%	n/N	%
Resistant to 2 antimicrobials	8/11	72.7	7/11	63.6
Resistant to 3 antimicrobials	5/7	71.4	5/7	71.4
Resistant to 4 antimicrobials	8/9	88.9	8/9	88.9
Resistant to 5 antimicrobials	8/8	100	8/8	100
Bacteremia with MDRSP	3/3	100	3/3	100

1011

1012

1013

1014

1015 **Clinical Safety Study of Rash**

1016
1017 To further characterize gemifloxacin-associated rash, which in early clinical
1018 studies appeared to be associated with age less than 40 and female gender, a clinical
1019 pharmacology study was conducted. The study enrolled 1,011 healthy female volunteers
1020 less than 40 years of age. Subjects were randomized in a 5:1 ratio to receive either
1021 FACTIVE 320 mg PO daily (819 subjects) or ciprofloxacin 500 mg PO twice daily for 10
1022 days (164 subjects). This study was designed to enroll subjects at high risk for rash
1023 (women <40 years of age and dosing beyond the recommended duration of therapy for
1024 FACTIVE [10 days]), and over estimates the risk to patients taking FACTIVE as
1025 prescribed. Subjects who received FACTIVE were 7 times more likely to develop rash
1026 than those who received ciprofloxacin. Of the 260 rashes in subjects receiving
1027 FACTIVE, the majority of the rashes were maculopapular and of mild to moderate
1028 severity; 7% of the rashes were reported as severe, and severity appeared to correlate
1029 with the extent of the rash. In 68% of the subjects reporting a severe rash and
1030 approximately 25% of all those reporting rash, >60% of the body surface area was
1031 involved; the characteristics of the rash were otherwise indistinguishable from those
1032 subjects reporting a mild rash. The histopathology was consistent with the clinical
1033 observation of uncomplicated exanthematous morbilliform eruption. Approximately
1034 11% of the rashes were described as being “urticaria-like”. There were no documented
1035 cases of hypersensitivity syndrome or findings suggestive of angioedema or other serious
1036 cutaneous reactions.

1037 The majority of rashes (81.9%) occurred on days 8 through 10 of the planned 10
1038 day course of FACTIVE; 2.7% of rash events occurred within one day of the start of
1039 dosing. The median duration of rash was 6 days. The rash resolved without treatment in
1040 the majority of subjects. Approximately 19% received antihistamines and 5% received
1041 steroids, although the therapeutic benefit of these therapies is uncertain.

1042 In the second part of this study after a 4 to 6 week wash out period, subjects
1043 developing a rash on FACTIVE were treated with ciprofloxacin (n=136) or placebo
1044 (n=50); 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash
1045 when treated with placebo. The cross sensitization rate to other fluoroquinolones was not
1046 evaluated in this clinical study. There was no evidence of sub-clinical sensitization to
1047 FACTIVE on a second exposure (i.e., subjects who had not developed a rash to
1048 FACTIVE in the first part of the study were not at higher risk of developing a rash to
1049 FACTIVE with a second exposure).

1050 There was no relationship between the incidence of rash and systemic exposure
1051 (C_{max} and AUC) to either gemifloxacin or its major metabolite, N-acetyl gemifloxacin.

1052
1053 **REFERENCES:** 1. Clinical and Laboratory Standards Institute. Methods for Dilution
1054 Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved
1055 Standard—Seventh Edition. Clinical and Laboratory Standards Institute document M7-
1056 A7, Vol. 26, No. 2, CLSI, Wayne, PA, January 2006. 2. Clinical and Laboratory
1057 Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility
1058 Tests—Ninth Edition. Clinical and Laboratory Standards Institute document M2-A9,
1059 Vol. 26, No. 1, CLSI, Wayne, PA, January 2006.

1060

1061 DATE OF REVISION May 2007
1062 © Oscient Pharmaceuticals Corporation 2007
1063 FACTIVE is a registered trademark of LG Life Sciences.

1064 **Rx only**

1065
1066 Manufactured for:
1067 Oscient Pharmaceuticals
1068 Waltham, MA 02451-1478 USA

1069
1070 Licensed from LG Life Sciences, Ltd. Seoul, Korea

1071
1072

1073 **Patient Information**

1074

1075 **FACTIVE®**

1076 **(gemifloxacin mesylate) Tablets**

1077

1078 This leaflet summarizes the most important information about FACTIVE. Read the
1079 Patient Information that comes with FACTIVE each time you get a new prescription.
1080 There may be new information. This leaflet does not list all benefits and risks of
1081 treatment and does not take the place of talking with your healthcare provider about your
1082 condition or your treatment.

1083

1084 **What is FACTIVE?**

1085 FACTIVE is an antibiotic. It is used to treat adults 18 years or older with bronchitis or
1086 pneumonia (lung infections) caused by certain bacteria (germs).

1087

1088 Sometimes, other germs called viruses infect the lungs. The common cold is a virus.
1089 FACTIVE, like other antibiotics, does not treat viruses.

1090

1091 **Who should not take FACTIVE?**

- 1092 • **Do not take FACTIVE if you are allergic to any of the ingredients in FACTIVE**
1093 **or to any antibiotic called a “quinolone”.** If you develop hives, difficulty
1094 breathing, or other symptoms of a severe allergic reaction, seek emergency treatment
1095 right away. If you develop a skin rash, stop taking FACTIVE and call your
1096 healthcare professional. The ingredients in FACTIVE are listed at the end of this
1097 leaflet. Ask your healthcare provider or pharmacist if you need a list of quinolone
1098 antibiotics.

1099

1100 **FACTIVE may not be right for you. Tell your healthcare provider if you:**

- 1101 • are pregnant, planning to become pregnant, or are breast feeding. The effects of
1102 FACTIVE on unborn children and nursing infants are unknown;
- 1103 • or any family members have a rare heart condition known as congenital prolongation
1104 of the QTc interval;
- 1105 • have low potassium or magnesium levels;
- 1106 • have a slow heart beat called bradycardia;

-
- 1107 • have had a recent heart attack;
1108 • have a history of seizures or epilepsy;
1109 • have kidney problems.

1110

1111 FACTIVE has not been studied in children under the age of 18. Quinolones, such as
1112 FACTIVE may cause joint problems (arthropathy) in children.

1113

1114 **What about other medicines I am taking?**

1115 Tell your healthcare provider about all the medicines you take including prescription and
1116 nonprescription medicines, vitamins, and dietary supplements. FACTIVE and other
1117 medicines may affect each other, causing serious side effects. **Be sure to tell your**
1118 **healthcare provider if you take:**

1119

- 1120 • medicines for your heart rhythm called “antiarrhythmics”
1121 • erythromycin
1122 • medicines for your mental health called “antipsychotics” or “tricyclic
1123 antidepressants”
1124 • medicines called “corticosteroids”, taken by mouth or by injection
1125 • medicines called “water pills” (diuretics) such as furosemide and
1126 hydrochlorothiazide;
1127 • medicines to thin your blood (called oral anticoagulants) such as Coumadin[®] or
1128 warfarin.

1129

1130 **How should I take FACTIVE?**

- 1131 • Take 1 FACTIVE tablet a day for 5 or 7 days, exactly as prescribed.
1132 • Take FACTIVE at the same time each day.
1133 • FACTIVE can be taken with or without food.
1134 • Swallow the FACTIVE tablet whole, and drink plenty of fluids with it. Do not chew
1135 the FACTIVE tablet.
1136 • If you miss a dose of FACTIVE, take it as soon as you remember. **Do not take more**
1137 **than 1 dose of FACTIVE in a day.**
1138 • To make sure all bacteria are killed, take all the medicine that was prescribed for you
1139 even if you begin to feel better.
1140 • Call your healthcare provider if your condition does not improve while taking
1141 FACTIVE.

1142

1143 **Do not take the following medicines within 3 hours before FACTIVE or 2 hours**
1144 **after FACTIVE.** They may interfere with the absorption of FACTIVE and may prevent
1145 it from working properly:

1146

- 1147 • antacids that contain magnesium or aluminum
1148 • ferrous sulfate (iron)
1149 • multivitamin that contains zinc or other metals
1150 • Videx[®] (didanosine)

1151

1152 **FACTIVE should be taken at least 2 hours before sucralfate.**

1153

1154 **What are possible side effects of FACTIVE?**

1155 FACTIVE is generally well tolerated. The most common side effects with FACTIVE
1156 include diarrhea, rash, nausea, headache, vomiting, stomach pain, dizziness, and a change
1157 in the way things taste in your mouth.

1158

1159 Rash occurs more commonly in women, especially those on hormone replacement
1160 therapy and anyone under 40. The likelihood of getting a rash increases if FACTIVE is
1161 taken for longer than 7 days. The rash is usually mild to moderate, but may occasionally
1162 be severe. If you get a rash while taking FACTIVE, stop FACTIVE, and call your
1163 healthcare provider right away.

1164

1165 **FACTIVE and other quinolone antibiotics may cause the following serious side**
1166 **effects:**

1167

- 1168 • **a rare heart problem known as prolongation of the QTc interval.** This condition
1169 can cause an abnormal heartbeat and result in sudden death. The chances of this
1170 event are increased in those with a family history of prolonged QT interval, low
1171 potassium (hypokalemia), and who are taking drugs to control heart rhythm, called
1172 Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic
1173 agents.

1174

1175 You should call your healthcare provider right away if you have any symptoms of
1176 prolongation of the QTc interval including:

- 1177 • heart palpitations (a change in the way your heart beats)
- 1178 • a loss of consciousness (fainting spells)

1179

- 1180 • **allergic reactions.** Get medical help right away if you develop hives, trouble
1181 breathing, wheezing, or other symptoms of a severe allergic reaction.

1182

- 1183 • **tendon problems including pain, swelling (tendonitis) or rupture (“tears”) of**
1184 **Achilles, shoulder or hand tendons.** The risk for tendon problems is higher if you
1185 are over 65 years old and/or are taking corticosteroids. If you experience pain,
1186 swelling, or rupture of a tendon, you should stop taking FACTIVE, avoid exercise
1187 and strenuous use of the affected area, and call your healthcare provider;

1188

- 1189 • **diarrhea** that usually ends after treatment is a common problem caused by
1190 antibiotics. A more serious form of diarrhea with inflammation of the colon
1191 (pseudomembranous colitis) can occur during or up to 2 months after the use of
1192 antibiotics. This has been reported with all antibiotics including with FACTIVE. If
1193 you develop a watery and bloody stool with or without stomach cramps and fever,
1194 contact your physician as soon as possible.

1195

-
- 1196 • **central nervous system problems** including body shakes (tremors), restless feeling,
1197 lightheaded feelings, confusion, and hallucinations (seeing or hearing things that are
1198 not there);
1199
- 1200 • **dizziness.** FACTIVE can make you dizzy. Do not drive or operate heavy machinery
1201 until you know how FACTIVE affects you.
1202
- 1203 • **phototoxicity.** FACTIVE may rarely make your skin sunburn more easily. Do not
1204 use a sunlamp or tanning bed while taking FACTIVE. Use a sunscreen and wear
1205 protective clothing if you must be out in the sun.
1206

1207 These are not all the side effects you may experience with FACTIVE. If you get any side
1208 effects that concern you, call your healthcare provider.
1209

1210 **How should I store Factive?**

- 1211 • Store FACTIVE at room temperature between 59° and 86° F (15° to 30° C). Protect
1212 from light.
1213 • **Keep FACTIVE and all medicines out of the reach of children.**
1214

1215 **General information about the safe and effective use of FACTIVE:**

1216
1217 Medicines are sometimes prescribed for conditions other than those described in patient
1218 information leaflets. Do not use FACTIVE for a condition for which it was not
1219 prescribed. Do not give FACTIVE to other people, even if they have the same symptoms
1220 that you have. It may harm them.
1221

1222 **What are the ingredients in FACTIVE?**

1223 Active ingredient: gemifloxacin
1224 Inactive ingredients: crospovidone, hydroxypropyl methycellulose, magnesium stearate,
1225 microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide.
1226

1227 **FACTIVE tablets are white to off-white and imprinted with GE 320 on both sides.**
1228

1229 **This leaflet summarizes the most important information about FACTIVE. If you would**
1230 **like more information, talk with your healthcare provider. You can ask your healthcare**
1231 **provider or pharmacist for information about FACTIVE that is written for healthcare**
1232 **professionals. For more information, visit our website at www.factive.com.**
1233

1234 **DATE OF REVISION** May 2007

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1237 **Rx only**

1238

1239 **Manufactured for:**

1240 Oscient Pharmaceuticals

1241 Waltham, MA 02451-1478 USA

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