

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEXIVA safely and effectively. See full prescribing information for LEXIVA.

LEXIVA (fosamprenavir calcium) Tablets and Oral Suspension Initial U.S. Approval: 2003

INDICATIONS AND USAGE

LEXIVA is an HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

DOSAGE AND ADMINISTRATION

- Therapy-Naive Adults: LEXIVA 1,400 mg twice daily; LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily; LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily; LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily. (2.1)
- Protease Inhibitor-Experienced Adults: LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily. (2.1)
- Pediatric Patients (2 to 18 years of age): Dosage should be calculated based on body weight (kg) and should not exceed adult dose. (2.2)
- Hepatic Impairment: Recommended adjustments for patients with mild, moderate, or severe hepatic impairment. (2.3)

Dosing Considerations

- LEXIVA Tablets may be taken with or without food. (2)
- LEXIVA Suspension: Adults should take without food; pediatric patients should take with food. (2)

DOSAGE FORMS AND STRENGTHS

700-mg tablets and 50-mg/mL oral suspension (3)

CONTRAINDICATIONS

- Hypersensitivity to LEXIVA or amprenavir (e.g., Stevens-Johnson syndrome). (4)
- Drugs highly dependent on CYP3A4 for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. (4)
- Review ritonavir contraindications when used in combination. (4)

WARNINGS AND PRECAUTIONS

- Certain drugs should not be coadministered with LEXIVA due to risk of serious or life-threatening adverse reactions. (5.1)

- LEXIVA should be discontinued for severe skin reactions including Stevens-Johnson syndrome. (5.2)
- LEXIVA should be used with caution in patients with a known sulfonamide allergy. (5.3)
- Use of higher than approved doses may lead to transaminase elevations. Patients with hepatitis B or C are at increased risk of transaminase elevations. (5.4)
- Patients receiving LEXIVA may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.5), immune reconstitution syndrome (5.6), redistribution/accumulation of body fat (5.7), and elevated triglyceride and cholesterol concentrations (5.8). Monitor cholesterol and triglycerides prior to therapy and periodically thereafter.
- Acute hemolytic anemia has been reported with amprenavir. (5.9)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.10)
- Nephrolithiasis: Cases of nephrolithiasis have been reported with fosamprenavir. (5.11)

ADVERSE REACTIONS

- In adults the most common adverse reactions (incidence greater than or equal to 4%) are diarrhea, rash, nausea, vomiting, headache. (6.1)
- Vomiting was more frequent in pediatrics than in adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coadministration of LEXIVA with drugs that induce CYP3A4 may decrease amprenavir (active metabolite) concentrations leading to potential loss of virologic activity. (7, 12.3)
- Coadministration with drugs that inhibit CYP3A4 may increase amprenavir concentrations. (7, 12.3)
- Coadministration of LEXIVA and ritonavir may result in clinically significant interactions with drugs metabolized by CYP2D6. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: May 2011

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 LEXIVA[®] is indicated in combination with other antiretroviral agents for the treatment of
4 human immunodeficiency virus (HIV-1) infection.

5 The following points should be considered when initiating therapy with LEXIVA plus
6 ritonavir in protease inhibitor-experienced patients:

- 7 • The protease inhibitor-experienced patient study was not large enough to reach a definitive
8 conclusion that LEXIVA plus ritonavir and lopinavir plus ritonavir are clinically equivalent
9 [see *Clinical Studies (14.2)*].
- 10 • Once-daily administration of LEXIVA plus ritonavir is not recommended for adult protease
11 inhibitor-experienced patients or any pediatric patients.

12 2 DOSAGE AND ADMINISTRATION

13 LEXIVA Tablets may be taken with or without food.

14 Adults should take LEXIVA Oral Suspension without food. Pediatric patients should take
15 LEXIVA Oral Suspension with food [see *Clinical Pharmacology (12.3)*]. If emesis occurs
16 within 30 minutes after dosing, re-dosing of LEXIVA Oral Suspension should occur.

17 Higher-than-approved dose combinations of LEXIVA plus ritonavir are not
18 recommended due to an increased risk of transaminase elevations [see *Overdosage (10)*].

19 When LEXIVA is used in combination with ritonavir, prescribers should consult the full
20 prescribing information for ritonavir.

21 2.1 Adults

22 Therapy-Naive Adults:

- 23 • LEXIVA 1,400 mg twice daily (without ritonavir).
- 24 • LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily.
- 25 • LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily.

26 Dosing of LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily is supported by
27 pharmacokinetic data [see *Clinical Pharmacology (12.3)*].

- 28 • LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily.

29 Dosing of LEXIVA 700 mg twice daily plus 100 mg ritonavir twice daily is supported by
30 pharmacokinetic and safety data [see *Clinical Pharmacology (12.3)*].

31 Protease Inhibitor-Experienced Adults:

- 32 • LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily

33 2.2 Pediatric Patients (Aged 2 to 18 Years)

34 The recommended dosage of LEXIVA in patients aged greater than or equal to 2 years
35 should be calculated based on body weight (kg) and should not exceed the recommended adult
36 dose. The data are insufficient to recommend: (1) once-daily dosing of LEXIVA alone or in
37 combination with ritonavir, and (2) any dosing of LEXIVA in therapy-experienced patients aged
38 2 to 5 years.

39 Therapy-Naive Aged 2 to 5 Years:

- 40 • LEXIVA Oral Suspension 30 mg/kg twice daily, not to exceed the adult dose of LEXIVA
41 1,400 mg twice daily.

42 Therapy-Naive Aged Greater Than or Equal to 6 Years:

- 43 • Either LEXIVA Oral Suspension 30 mg/kg twice daily not to exceed the adult dose of
44 LEXIVA 1,400 mg twice daily or LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg
45 twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice
46 daily.

47 Therapy-Experienced Aged Greater Than or Equal to 6 Years:

- 48 • LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg administered twice daily not to
49 exceed the adult dose of LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily.

50 Other Dosing Considerations:

- 51 • When administered without ritonavir, the adult regimen of LEXIVA Tablets 1,400 mg twice
52 daily may be used for pediatric patients weighing at least 47 kg.
53 • When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric
54 patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients
55 weighing at least 33 kg.

56 **2.3 Patients With Hepatic Impairment**

57 *See Clinical Pharmacology (12.3).*

58 Mild Hepatic Impairment (Child-Pugh Score Ranging From 5 to 6): LEXIVA
59 should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir
60 (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or
61 protease inhibitor-experienced).

62 Moderate Hepatic Impairment (Child-Pugh Score Ranging From 7 to 9): LEXIVA
63 should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir
64 (therapy-naive), or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or
65 protease inhibitor-experienced).

66 Severe Hepatic Impairment (Child-Pugh Score Ranging From 10 to 15): LEXIVA
67 should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir
68 (therapy-naive) or 300 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or
69 protease inhibitor-experienced).

70 **3 DOSAGE FORMS AND STRENGTHS**

71 LEXIVA Tablets, 700 mg, are pink, film-coated, capsule-shaped, biconvex tablets with
72 “GX LL7” debossed on one face.

73 LEXIVA Oral Suspension, 50 mg/mL, is a white to off-white suspension that has a
74 characteristic grape-bubblegum-peppermint flavor.

75 **4 CONTRAINDICATIONS**

76 LEXIVA is contraindicated:

- 77 • in patients with previously demonstrated clinically significant hypersensitivity (e.g.,
78 Stevens-Johnson syndrome) to any of the components of this product or to amprenavir.
79 • when coadministered with drugs that are highly dependent on CYP3A4 for clearance and for
80 which elevated plasma concentrations are associated with serious and/or life-threatening
81 events (Table 1).
82

83 **Table 1. Drugs Contraindicated With LEXIVA (Information in the table applies to**
 84 **LEXIVA with or without ritonavir, unless otherwise indicated.)**

Drug Class/Drug Name	Clinical Comment
Alpha 1-adrenoreceptor antagonist: Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmics: Flecainide, propafenone	POTENTIAL for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics if LEXIVA is co-prescribed with ritonavir .
Antimycobacterials: Rifampin ^a	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	POTENTIAL for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	POTENTIAL for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (<i>hypericum perforatum</i>)	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
HMG co-reductase inhibitors: Lovastatin, simvastatin	POTENTIAL for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	POTENTIAL for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine ^a	May lead to loss of virologic response and possible resistance to delavirdine.
PDE5 inhibitor: Sildenafil (REVATIO [®]) (for treatment of pulmonary arterial hypertension)	A safe and effective dose has not been established when used with LEXIVA. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).
Sedative/hypnotics: Midazolam, triazolam	POTENTIAL for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

85 ^a See *Clinical Pharmacology (12.3) Tables 10, 11, 12, or 13 for magnitude of interaction.*
 86

- 87 • when coadministered with ritonavir in patients receiving the antiarrhythmic agents flecainide
88 and propafenone. If LEXIVA is coadministered with ritonavir, reference should be made to
89 the full prescribing information for ritonavir for additional contraindications.

90 **5 WARNINGS AND PRECAUTIONS**

91 **5.1 Drug Interactions**

92 See Table 1 for listings of drugs that are contraindicated due to potentially
93 life-threatening adverse events, significant drug interactions, or due to loss of virologic activity
94 [see *Contraindications (4)*, *Drug Interactions (7.2)*]. See Table 6 for a listing of established and
95 other potentially significant drug interactions [see *Drug Interactions (7.3)*].

96 **5.2 Skin Reactions**

97 Severe and life-threatening skin reactions, including 1 case of Stevens-Johnson syndrome
98 among 700 patients treated with LEXIVA in clinical studies. Treatment with LEXIVA should be
99 discontinued for severe or life-threatening rashes and for moderate rashes accompanied by
100 systemic symptoms [see *Adverse Reactions (6)*].

101 **5.3 Sulfa Allergy**

102 LEXIVA should be used with caution in patients with a known sulfonamide allergy.
103 Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs
104 in the sulfonamide class and fosamprenavir is unknown. In a clinical study of LEXIVA used as
105 the sole protease inhibitor, rash occurred in 2 of 10 patients (20%) with a history of sulfonamide
106 allergy compared with 42 of 126 patients (33%) with no history of sulfonamide allergy. In
107 2 clinical studies of LEXIVA plus low-dose ritonavir, rash occurred in 8 of 50 patients (16%)
108 with a history of sulfonamide allergy compared with 50 of 412 patients (12%) with no history of
109 sulfonamide allergy.

110 **5.4 Hepatic Toxicity**

111 Use of LEXIVA with ritonavir at higher-than-recommended dosages may result in
112 transaminase elevations and should not be used [see *Dosage and Administration (2)*, *Overdosage*
113 *(10)*]. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to
114 treatment may be at increased risk for developing or worsening of transaminase elevations.
115 Appropriate laboratory testing should be conducted prior to initiating therapy with LEXIVA and
116 patients should be monitored closely during treatment.

117 **5.5 Diabetes/Hyperglycemia**

118 New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and
119 hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients
120 receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments
121 of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic
122 ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy,
123 hyperglycemia persisted in some cases. Because these events have been reported voluntarily
124 during clinical practice, estimates of frequency cannot be made and causal relationships between
125 protease inhibitor therapy and these events have not been established.

126 **5.6 Immune Reconstitution Syndrome**

127 Immune reconstitution syndrome has been reported in patients treated with combination
128 antiretroviral therapy, including LEXIVA. During the initial phase of combination antiretroviral
129 treatment, patients whose immune systems respond may develop an inflammatory response to
130 indolent or residual opportunistic infections (such as *Mycobacterium avium* infection,
131 cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may
132 necessitate further evaluation and treatment.

133 **5.7 Fat Redistribution**

134 Redistribution/accumulation of body fat, including central obesity, dorsocervical fat
135 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and
136 “cushingoid appearance,” have been observed in patients receiving antiretroviral therapy,
137 including LEXIVA. The mechanism and long-term consequences of these events are currently
138 unknown. A causal relationship has not been established.

139 **5.8 Lipid Elevations**

140 Treatment with LEXIVA plus ritonavir has resulted in increases in the concentration of
141 triglycerides and cholesterol [*see Adverse Reactions (6)*]. Triglyceride and cholesterol testing
142 should be performed prior to initiating therapy with LEXIVA and at periodic intervals during
143 therapy. Lipid disorders should be managed as clinically appropriate [*see Drug Interactions (7)*].

144 **5.9 Hemolytic Anemia**

145 Acute hemolytic anemia has been reported in a patient treated with amprenavir.

146 **5.10 Patients With Hemophilia**

147 There have been reports of spontaneous bleeding in patients with hemophilia A and B
148 treated with protease inhibitors. In some patients, additional factor VIII was required. In many of
149 the reported cases, treatment with protease inhibitors was continued or restarted. A causal
150 relationship between protease inhibitor therapy and these episodes has not been established.

151 **5.11 Nephrolithiasis**

152 Cases of nephrolithiasis were reported during postmarketing surveillance in HIV-infected
153 patients receiving LEXIVA. Because these events were reported voluntarily during clinical
154 practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur,
155 temporary interruption or discontinuation of therapy may be considered.

156 **5.12 Resistance/Cross-Resistance**

157 Because the potential for HIV cross-resistance among protease inhibitors has not been
158 fully explored, it is unknown what effect therapy with LEXIVA will have on the activity of
159 subsequently administered protease inhibitors. LEXIVA has been studied in patients who have
160 experienced treatment failure with protease inhibitors [*see Clinical Studies (14.2)*].

161 **6 ADVERSE REACTIONS**

- 162 • Severe or life-threatening skin reactions have been reported with the use of LEXIVA [*see*
163 *Warnings and Precautions (5.2)*].

- 164 • The most common moderate to severe adverse reactions in clinical studies of LEXIVA were
165 diarrhea, rash, nausea, vomiting, and headache.
- 166 • Treatment discontinuation due to adverse events occurred in 6.4% of patients receiving
167 LEXIVA and in 5.9% of patients receiving comparator treatments. The most common adverse
168 reactions leading to discontinuation of LEXIVA (incidence less than or equal to 1% of
169 patients) included diarrhea, nausea, vomiting, AST increased, ALT increased, and rash.

170 **6.1 Clinical Trials**

171 Adults: The data for the 3 active-controlled clinical trials described below reflect
172 exposure of 700 HIV-1 infected patients to LEXIVA Tablets, including 599 patients exposed to
173 LEXIVA for greater than 24 weeks, and 409 patients exposed for greater than 48 weeks. The
174 population age ranged from 17 to 72 years. Of these patients, 26% were female, 51% Caucasian,
175 31% black, 16% American Hispanic, and 70% were antiretroviral-naive. Sixty-one percent received
176 LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily, 24% received LEXIVA
177 1,400 mg twice daily, and 15% received LEXIVA 700 mg twice daily plus ritonavir 100 mg
178 twice daily.

179 Because clinical trials are conducted under widely varying conditions, adverse reaction
180 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
181 trials of another drug and may not reflect the rates observed in clinical practice.

182 Selected adverse reactions reported during the clinical efficacy studies of LEXIVA are
183 shown in Tables 2 and 3. Each table presents adverse reactions of moderate or severe intensity in
184 patients treated with combination therapy for up to 48 weeks.

185

186 **Table 2. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater Than**
 187 **or Equal to 2% of Antiretroviral-Naive Adult Patients**

Adverse Reaction	APV30001 ^a		APV30002 ^a	
	LEXIVA 1,400 mg b.i.d. (n = 166)	Nelfinavir 1,250 mg b.i.d. (n = 83)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d. (n = 322)	Nelfinavir 1,250 mg b.i.d. (n = 327)
Gastrointestinal				
Diarrhea	5%	18%	10%	18%
Nausea	7%	4%	7%	5%
Vomiting	2%	4%	6%	4%
Abdominal pain	1%	0%	2%	2%
Skin				
Rash	8%	2%	3%	2%
General disorders				
Fatigue	2%	1%	4%	2%
Nervous system				
Headache	2%	4%	3%	3%

188 ^aAll patients also received abacavir and lamivudine twice daily.

189
 190 **Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater Than**
 191 **or Equal to 2% of Protease Inhibitor-Experienced Adult Patients (Study APV30003)**

Adverse Reaction	LEXIVA 700 mg b.i.d./ Ritonavir 100 mg b.i.d. ^a (n = 106)	Lopinavir 400 mg b.i.d./ Ritonavir 100 mg b.i.d. ^a (n = 103)
Gastrointestinal		
Diarrhea	13%	11%
Nausea	3%	9%
Vomiting	3%	5%
Abdominal pain	<1%	2%
Skin		
Rash	3%	0%
Nervous system		
Headache	4%	2%

192 ^aAll patients also received 2 reverse transcriptase inhibitors.

193
 194 Skin rash (without regard to causality) occurred in approximately 19% of patients treated
 195 with LEXIVA in the pivotal efficacy studies. Rashes were usually maculopapular and of mild or
 196 moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of

197 LEXIVA and had a median duration of 13 days. Skin rash led to discontinuation of LEXIVA in
 198 less than 1% of patients. In some patients with mild or moderate rash, dosing with LEXIVA was
 199 often continued without interruption; if interrupted, reintroduction of LEXIVA generally did not
 200 result in rash recurrence.

201 The percentages of patients with Grade 3 or 4 laboratory abnormalities in the clinical
 202 efficacy studies of LEXIVA are presented in Tables 4 and 5.

203

204 **Table 4. Grade 3/4 Laboratory Abnormalities Reported in Greater Than or Equal to 2% of**
 205 **Antiretroviral-Naive Adult Patients in Studies APV30001 and APV30002**

Laboratory Abnormality	APV30001 ^a		APV30002 ^a	
	LEXIVA 1,400 mg b.i.d. (n = 166)	Nelfinavir 1,250 mg b.i.d. (n = 83)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d. (n = 322)	Nelfinavir 1,250 mg b.i.d. (n = 327)
ALT (>5 x ULN)	6%	5%	8%	8%
AST (>5 x ULN)	6%	6%	6%	7%
Serum lipase (>2 x ULN)	8%	4%	6%	4%
Triglycerides ^b (>750 mg/dL)	0%	1%	6%	2%
Neutrophil count, absolute (<750 cells/mm ³)	3%	6%	3%	4%

206 ^aAll patients also received abacavir and lamivudine twice daily.

207 ^bFasting specimens.

208 ULN = Upper limit of normal.

209

210 The incidence of Grade 3 or 4 hyperglycemia in antiretroviral-naive patients who
 211 received LEXIVA in the pivotal studies was less than 1%.

212

213 **Table 5. Grade 3/4 Laboratory Abnormalities Reported in Greater Than or Equal to 2% of**
 214 **Protease Inhibitor-Experienced Adult Patients in Study APV30003**

Laboratory Abnormality	LEXIVA 700 mg b.i.d./ Ritonavir 100 mg b.i.d. ^a (n = 104)	Lopinavir 400 mg b.i.d./ Ritonavir 100 mg b.i.d. ^a (n = 103)
Triglycerides ^b (>750 mg/dL)	11% ^c	6% ^c
Serum lipase (>2 x ULN)	5%	12%
ALT (>5 x ULN)	4%	4%
AST (>5 x ULN)	4%	2%
Glucose (>251 mg/dL)	2% ^c	2% ^c

215 ^aAll patients also received 2 reverse transcriptase inhibitors.

216 ^bFasting specimens.

217 ^cn = 100 for LEXIVA plus ritonavir, n = 98 for lopinavir plus ritonavir.

218 ULN = Upper limit of normal.

219

220 **Pediatric Patients:** LEXIVA with and without ritonavir was studied in 144 pediatric
 221 patients aged 2 to 18 years in 2 open-label studies. Safety information from 75 pediatric patients
 222 receiving LEXIVA twice daily with or without ritonavir follows.

223 All adverse events regardless of causality, all drug-related adverse events, and all
 224 laboratory events occurred with similar frequency in pediatrics compared with adults, with the
 225 exception of vomiting. Vomiting, regardless of causality, occurred more frequently among
 226 pediatric patients receiving LEXIVA twice daily with ritonavir ([30%] all aged between 2 and
 227 18 years) and without ritonavir ([56%] all aged between 2 and 5 years) compared with adults
 228 receiving LEXIVA twice daily with ritonavir (10%) and without ritonavir (16%). The median
 229 duration of drug-related vomiting episodes was 1 day (range: 1 to 62 days). Vomiting required
 230 temporary dose interruptions in 4 pediatric patients and was treatment-limiting in 1 pediatric
 231 patient, all of whom were receiving LEXIVA twice daily with ritonavir.

232 **6.2 Postmarketing Experience**

233 In addition to adverse reactions reported from clinical trials, the following reactions have
 234 been identified during post-approval use of LEXIVA. Because they are reported voluntarily from
 235 a population of unknown size, estimates of frequency cannot be made. These reactions have been
 236 chosen for inclusion due to a combination of their seriousness, frequency of reporting, or
 237 potential causal connection to LEXIVA.

238 **Cardiac Disorders:** Myocardial infarction.

239 **Metabolism and Nutrition Disorders:** Hypercholesterolemia.

240 **Nervous System Disorders:** Oral paresthesia.

241 **Skin and Subcutaneous Tissue Disorders:** Angioedema.

242 **Urogenital:** Nephrolithiasis.

243 **7 DRUG INTERACTIONS**

244 *See also Contraindications (4), Clinical Pharmacology (12.3).*

245 If LEXIVA is used in combination with ritonavir, see full prescribing information for
246 ritonavir for additional information on drug interactions.

247 **7.1 CYP Inhibitors and Inducers**

248 Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of cytochrome P450
249 3A4 metabolism and therefore should not be administered concurrently with medications with
250 narrow therapeutic windows that are substrates of CYP3A4. Data also suggest that amprenavir
251 induces CYP3A4.

252 Amprenavir is metabolized by CYP3A4. Coadministration of LEXIVA and drugs that
253 induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its
254 therapeutic effect. Coadministration of LEXIVA and drugs that inhibit CYP3A4 may increase
255 amprenavir concentrations and increase the incidence of adverse effects.

256 The potential for drug interactions with LEXIVA changes when LEXIVA is
257 coadministered with the potent CYP3A4 inhibitor ritonavir. The magnitude of
258 CYP3A4-mediated drug interactions (effect on amprenavir or effect on coadministered drug)
259 may change when LEXIVA is coadministered with ritonavir. Because ritonavir is a CYP2D6
260 inhibitor, clinically significant interactions with drugs metabolized by CYP2D6 are possible
261 when coadministered with LEXIVA plus ritonavir.

262 There are other agents that may result in serious and/or life-threatening drug interactions
263 [*see Contraindications (4)*].

264 **7.2 Drugs That Should Not Be Coadministered With LEXIVA**

265 *See Contraindications (4).*

266 **7.3 Established and Other Potentially Significant Drug Interactions**

267 Table 6 provides a listing of established or potentially clinically significant drug
 268 interactions. Information in the table applies to LEXIVA with or without ritonavir, unless
 269 otherwise indicated.

270

271 **Table 6. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		
Non-nucleoside reverse transcriptase inhibitor: Efavirenz ^a	LEXIVA: ↓Amprenavir LEXIVA/ritonavir: ↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with LEXIVA/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with LEXIVA plus ritonavir twice daily.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine ^a	LEXIVA: ↓Amprenavir ↑Nevirapine LEXIVA/ritonavir: ↓Amprenavir ↑Nevirapine	Coadministration of nevirapine and LEXIVA without ritonavir is not recommended. No dosage adjustment required when nevirapine is administered with LEXIVA/ritonavir twice daily. The combination of nevirapine administered with LEXIVA/ritonavir once-daily regimen has not been studied.
HIV protease inhibitor: Atazanavir ^a	LEXIVA: Interaction has not been evaluated. LEXIVA/ritonavir: ↓Atazanavir ↔Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.

<p>HIV protease inhibitors: Indinavir^a, nelfinavir^a</p>	<p>LEXIVA: ↑Amprenavir</p> <p>Effect on indinavir and nelfinavir is not well established.</p> <p>LEXIVA/ritonavir: Interaction has not been evaluated.</p>	<p>Appropriate doses of the combinations with respect to safety and efficacy have not been established.</p>
<p>HIV protease inhibitors: Lopinavir/ritonavir^a</p>	<p>↓Amprenavir ↓Lopinavir</p>	<p>An increased rate of adverse events has been observed. Appropriate doses of the combinations with respect to safety and efficacy have not been established.</p>
<p>HIV protease inhibitor: Saquinavir^a</p>	<p>LEXIVA: ↓Amprenavir</p> <p>Effect on saquinavir is not well established.</p> <p>LEXIVA/ritonavir: Interaction has not been evaluated.</p>	<p>Appropriate doses of the combination with respect to safety and efficacy have not been established.</p>
<p>HIV integrase inhibitor: Raltegravir^a</p>	<p>LEXIVA: ↓Amprenavir ↓Raltegravir</p> <p>LEXIVA/ritonavir: ↓Amprenavir ↓Raltegravir</p>	<p>Appropriate doses of the combination with respect to safety and efficacy have not been established [<i>see Clinical Pharmacology (12.3)</i>].</p>
Other Agents		
<p>Antiarrhythmics: Amiodarone, bepridil, lidocaine (systemic), and quinidine</p>	<p>↑Antiarrhythmics</p>	<p>Use with caution. Increased exposure may be associated with life-threatening reactions such as cardiac arrhythmias. Therapeutic concentration monitoring, if available, is recommended for</p>

		antiarrhythmics.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin Phenytoin ^a	LEXIVA: ↓Amprenavir LEXIVA/ritonavir: ↑Amprenavir ↓Phenytoin	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Plasma phenytoin concentrations should be monitored and phenytoin dose should be increased as appropriate. No change in LEXIVA/ritonavir dose is recommended.
Antidepressant: Paroxetine, trazodone	↓Paroxetine ↑Trazodone	Coadministration of paroxetine with LEXIVA/ritonavir significantly decreased plasma levels of paroxetine. Any paroxetine dose adjustment should be guided by clinical effect (tolerability and efficacy). Concomitant use of trazodone and LEXIVA with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as LEXIVA, the combination should be used with caution and a lower dose of trazodone should be considered.

<p>Antifungals: Ketoconazole^a, itraconazole</p>	<p>↑Ketoconazole ↑Itraconazole</p>	<p>Increase monitoring for adverse events. LEXIVA: Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day. LEXIVA/ritonavir: High doses of ketoconazole or itraconazole (greater than 200 mg/day) are not recommended.</p>
<p>Anti-gout: Colchicine</p>	<p>↑Colchicine</p>	<p>Patients with renal or hepatic impairment should not be given colchicine with LEXIVA/ritonavir.</p> <p>LEXIVA/ritonavir and coadministration of colchicine:</p> <p>Treatment of gout flares: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p>Treatment of familial Mediterranean fever (FMF): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p> <p>LEXIVA and coadministration of colchicine:</p> <p>Treatment of gout flares: 1.2 mg (2 tablets) x 1 dose. Dose to be</p>

		<p>repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg twice a day or 0.6 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once a day.</p> <p>Treatment of FMF: Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day).</p>
<p>Antimycobacterial: Rifabutin^a</p>	<p>↑Rifabutin and rifabutin metabolite</p>	<p>A complete blood count should be performed weekly and as clinically indicated to monitor for neutropenia.</p> <p>LEXIVA: A dosage reduction of rifabutin by at least half the recommended dose is required.</p> <p>LEXIVA/ritonavir: Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).</p>
<p>Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam</p>	<p>↑Benzodiazepines</p>	<p>Clinical significance is unknown. A decrease in benzodiazepine dose may be needed.</p>
<p>Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine</p>	<p>↑Calcium channel blockers</p>	<p>Use with caution. Clinical monitoring of patients is recommended.</p>
<p>Corticosteroid: Dexamethasone</p>	<p>↓Amprenavir</p>	<p>Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations.</p>
<p>Endothelin receptor</p>	<p>↑Bosentan</p>	<p>Coadministration of bosentan in patients</p>

<p>antagonists: Bosentan</p>		<p>on LEXIVA:</p> <p>In patients who have been receiving LEXIVA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p> <p>Coadministration of LEXIVA in patients on bosentan:</p> <p>Discontinue use of bosentan at least 36 hours prior to initiation of LEXIVA.</p> <p>After at least 10 days following the initiation of LEXIVA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p>
<p>Histamine H₂-receptor antagonists: Cimetidine, famotidine, nizatidine, ranitidine^a</p>	<p>LEXIVA: ↓Amprenavir</p> <p>LEXIVA/ritonavir: Interaction not evaluated</p>	<p>Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations.</p>
<p>HMG-CoA reductase inhibitors: Atorvastatin^a, rosuvastatin</p>	<p>↑Atorvastatin ↑Rosuvastatin</p>	<p>Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin or pravastatin.</p>
<p>Immunosuppressants: Cyclosporine, tacrolimus, rapamycin</p>	<p>↑Immunosuppressants</p>	<p>Therapeutic concentration monitoring is recommended for immunosuppressant agents.</p>
<p>Inhaled beta agonist: Salmeterol</p>	<p>↑Salmeterol</p>	<p>Concurrent administration of salmeterol with LEXIVA is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.</p>
<p>Inhaled/nasal steroid: Fluticasone</p>	<p>LEXIVA: ↑Fluticasone</p>	<p>Use with caution. Consider alternatives to fluticasone, particularly for long-term use.</p>

	LEXIVA/ritonavir: ↑Fluticasone	May result in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone. Coadministration of fluticasone and LEXIVA/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
Narcotic analgesic: Methadone	↓Methadone	Data suggest that the interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms.
Oral contraceptives: Ethinyl estradiol/norethindrone ^a	LEXIVA: ↓Amprenavir ↓Ethinyl estradiol LEXIVA/ritonavir: ↓Ethinyl estradiol	Alternative methods of non-hormonal contraception are recommended. May lead to loss of virologic response. ^a Increased risk of transaminase elevations. No data are available on the use of LEXIVA/ritonavir with other hormonal therapies, such as hormone replacement therapy (HRT) for postmenopausal women.
PDE5 inhibitors: Sildenafil, tadalafil, vardenafil	↑Sildenafil ↑Tadalafil ↑Vardenafil	May result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism. <u>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):</u> <ul style="list-style-type: none"> • Use of sildenafil (REVATIO) is contraindicated when used for the treatment of PAH-[see <i>Contraindications (4)</i>].

		<ul style="list-style-type: none">• <u>The following dose adjustments are recommended for use of tadalafil (ADCIRCA™) with LEXIVA:</u> <p><u>Coadministration of ADCIRCA in patients on LEXIVA:</u></p> <p>In patients receiving LEXIVA for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Coadministration of LEXIVA in patients on ADCIRCA:</u></p> <p>Avoid use of ADCIRCA during the initiation of LEXIVA. Stop ADCIRCA at least 24 hours prior to starting LEXIVA. After at least one week following the initiation of LEXIVA, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Use of PDE5 inhibitors for erectile dysfunction:</u></p> <p>LEXIVA: Sildenafil: 25 mg every 48 hours. Tadalafil: no more than 10 mg every 72 hours. Vardenafil: no more than 2.5 mg every 24 hours.</p> <p>LEXIVA/ritonavir: Sildenafil: 25 mg every 48 hours. Tadalafil: no more than 10 mg every 72 hours. Vardenafil: no more than 2.5 mg every 72 hours.</p>
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		Use with increased monitoring for adverse events.
Proton pump inhibitors: Esomeprazole ^a , lansoprazole, omeprazole, pantoprazole, rabeprazole	LEXIVA: ↔Amprenavir ↑Esomeprazole LEXIVA/ritonavir: ↔Amprenavir ↔Esomeprazole	Proton pump inhibitors can be administered at the same time as a dose of LEXIVA with no change in plasma amprenavir concentrations.
Tricyclic antidepressants: Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants.

272 ^aSee *Clinical Pharmacology (12.3) Tables 10, 11, 12, or 13 for magnitude of interaction.*

273 **8 USE IN SPECIFIC POPULATIONS**

274 **8.1 Pregnancy**

275 Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed
276 from day 6 to day 17 of gestation) and rabbits (dosed from day 7 to day 20 of gestation).
277 Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on
278 embryo-fetal development; however, the incidence of abortion was increased in rabbits that were
279 administered fosamprenavir. Systemic exposures (AUC_{0-24 hr}) to amprenavir at these dosages
280 were 0.8 (rabbits) to 2 (rats) times the exposures in humans following administration of the
281 maximum recommended human dose (MRHD) of fosamprenavir alone or 0.3 (rabbits) to 0.7
282 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir in
283 combination with ritonavir. In contrast, administration of amprenavir was associated with
284 abortions and an increased incidence of minor skeletal variations resulting from deficient
285 ossification of the femur, humerus, and trochlea, in pregnant rabbits at the tested dose;
286 approximately one-twentieth the exposure seen at the recommended human dose.

287 The mating and fertility of the F₁ generation born to female rats given fosamprenavir was
288 not different from control animals; however, fosamprenavir did cause a reduction in both pup
289 survival and body weights. Surviving F₁ female rats showed an increased time to successful
290 mating, an increased length of gestation, a reduced number of uterine implantation sites per litter,
291 and reduced gestational body weights compared with control animals. Systemic exposure
292 (AUC_{0-24 hr}) to amprenavir in the F₀ pregnant rats was approximately 2 times higher than
293 exposures in humans following administration of the MRHD of fosamprenavir alone or
294 approximately the same as those seen in humans following administration of the MRHD of
295 fosamprenavir in combination with ritonavir.

296 There are no adequate and well-controlled studies in pregnant women. LEXIVA should
297 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

298 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant
299 women exposed to LEXIVA, an Antiretroviral Pregnancy Registry has been established.
300 Physicians are encouraged to register patients by calling 1-800-258-4263.

301 **8.3 Nursing Mothers**

302 The Centers for Disease Control and Prevention recommend that HIV-infected mothers
303 not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not
304 known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating
305 rats. Because of both the potential for HIV transmission and the potential for serious adverse
306 reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving
307 LEXIVA.

308 **8.4 Pediatric Use**

309 The safety, pharmacokinetic profile, and virologic response of LEXIVA Oral Suspension
310 and Tablets were evaluated in pediatric patients aged 2 to 18 years in 2 open-label studies [*see*
311 *Clinical Studies (14.3)*]. No data are available for pediatric patients younger than 2 years.

312 The adverse reaction profile seen in pediatrics was similar to that seen in adults.
313 Vomiting, regardless of causality, was more frequent in pediatrics than in adults [*see Adverse*
314 *Reactions (6.1)*].

315 **8.5 Geriatric Use**

316 Clinical studies of LEXIVA did not include sufficient numbers of patients aged 65 and
317 over to determine whether they respond differently from younger adults. In general, dose
318 selection for an elderly patient should be cautious, reflecting the greater frequency of decreased
319 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

320 **8.6 Hepatic Impairment**

321 Amprenavir is principally metabolized by the liver; therefore, caution should be exercised
322 when administering LEXIVA to patients with hepatic impairment because amprenavir
323 concentrations may be increased [*see Clinical Pharmacology (12.3)*]. Patients with impaired
324 hepatic function receiving LEXIVA with or without concurrent ritonavir require dose reduction
325 [*see Dosage and Administration (2.3)*].

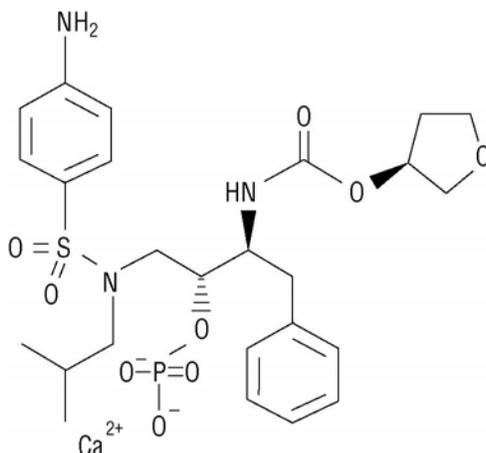
326 **10 OVERDOSAGE**

327 In a healthy volunteer repeat-dose pharmacokinetic study evaluating high-dose
328 combinations of LEXIVA plus ritonavir, an increased frequency of Grade 2/3 ALT elevations
329 (greater than 2.5 x ULN) was observed with LEXIVA 1,400 mg twice daily plus ritonavir
330 200 mg twice daily (4 of 25 subjects). Concurrent Grade 1/2 elevations in AST (greater than 1.25
331 x ULN) were noted in 3 of these 4 subjects. These transaminase elevations resolved following
332 discontinuation of dosing.

333 There is no known antidote for LEXIVA. It is not known whether amprenavir can be
334 removed by peritoneal dialysis or hemodialysis. If overdose occurs, the patient should be
335 monitored for evidence of toxicity and standard supportive treatment applied as necessary.

336 **11 DESCRIPTION**

337 LEXIVA (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of HIV
338 protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-
339 [[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonoxy) propylcarbamate
340 monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*)
341 configuration. It has a molecular formula of C₂₅H₃₄CaN₃O₉PS and a molecular weight of 623.7.
342 It has the following structural formula:
343



344
345
346 Fosamprenavir calcium is a white to cream-colored solid with a solubility of
347 approximately 0.31 mg/mL in water at 25°C.
348 LEXIVA Tablets are available for oral administration in a strength of 700 mg of
349 fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir).
350 Each 700-mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose
351 sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet
352 film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and
353 triacetin.

354 LEXIVA Oral Suspension is available in a strength of 50 mg/mL of fosamprenavir as
355 fosamprenavir calcium equivalent to approximately 43 mg of amprenavir. LEXIVA Oral
356 Suspension is a white to off-white suspension with a grape-bubblegum-peppermint flavor. Each
357 one milliliter (1 mL) contains the inactive ingredients artificial grape-bubblegum flavor, calcium
358 chloride dihydrate, hypromellose, methylparaben, natural peppermint flavor, polysorbate 80,
359 propylene glycol, propylparaben, purified water, and sucralose.

360 **12 CLINICAL PHARMACOLOGY**

361 **12.1 Mechanism of Action**

362 Fosamprenavir is an antiviral agent [see *Clinical Pharmacology (12.4)*].

363 **12.3 Pharmacokinetics**

364 The pharmacokinetic properties of amprenavir after administration of LEXIVA, with or
365 without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-infected

366 patients; no substantial differences in steady-state amprenavir concentrations were observed
367 between the 2 populations.

368 The pharmacokinetic parameters of amprenavir after administration of LEXIVA (with
369 and without concomitant ritonavir) are shown in Table 7.

370

371 **Table 7. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
372 **Parameters in Adults**

Regimen	C _{max} (mcg/mL)	T _{max} (hours) ^a	AUC ₂₄ (mcg•hr/mL)	C _{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 1,400 mg q.d. plus Ritonavir 100 mg q.d.	7.93 (7.25-8.68)	1.5 (0.75-5.0)	66.4 (61.1-72.1)	0.86 (0.74-1.01)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

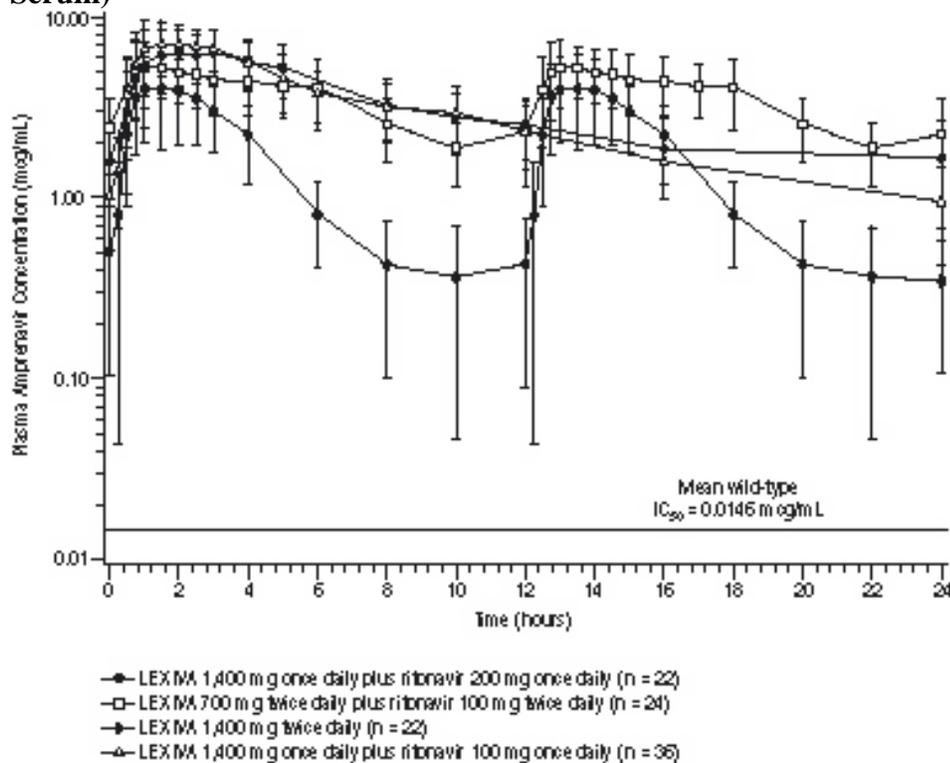
373 ^aData shown are median (range).

374

375 The mean plasma amprenavir concentrations of the dosing regimens over the dosing
376 intervals are displayed in Figure 1.

377

378 **Figure 1. Mean (\pm SD) Steady-State Plasma Amprenavir Concentrations and Mean IC_{50}**
 379 **Values Against HIV from Protease Inhibitor-Naive Patients (in the Absence of Human**
 380 **Serum)**



381
382

383 **Absorption and Bioavailability:** After administration of a single dose of LEXIVA to
 384 HIV-1-infected patients, the time to peak amprenavir concentration (T_{max}) occurred between 1.5
 385 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after
 386 administration of LEXIVA in humans has not been established.

387 After administration of a single 1,400-mg dose in the fasted state, LEXIVA Oral
 388 Suspension (50 mg/mL) and LEXIVA Tablets (700 mg) provided similar amprenavir exposures
 389 (AUC), however, the C_{max} of amprenavir after administration of the suspension formulation was
 390 14.5% higher compared with the tablet.

391 **Effects of Food on Oral Absorption:** Administration of a single 1,400-mg dose of
 392 LEXIVA Tablets in the fed state (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams
 393 protein, 58 grams carbohydrate) compared with the fasted state was associated with no
 394 significant changes in amprenavir C_{max} , T_{max} , or $AUC_{0-\infty}$ [see *Dosage and Administration (2)*].

395 Administration of a single 1,400-mg dose of LEXIVA Oral Suspension in the fed state
 396 (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate)
 397 compared with the fasted state was associated with a 46% reduction in C_{max} , a 0.72-hour delay in
 398 T_{max} , and a 28% reduction in amprenavir $AUC_{0-\infty}$.

399 **Distribution:** In vitro, amprenavir is approximately 90% bound to plasma proteins,
 400 primarily to α_1 -acid glycoprotein. In vitro, concentration-dependent binding was observed

401 over the concentration range of 1 to 10 mcg/mL, with decreased binding at higher
402 concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as
403 amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher
404 concentrations.

405 **Metabolism:** After oral administration, fosamprenavir is rapidly and almost completely
406 hydrolyzed to amprenavir and inorganic phosphate prior to reaching the systemic circulation.
407 This occurs in the gut epithelium during absorption. Amprenavir is metabolized in the liver by
408 the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from
409 oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized
410 metabolites have been identified as minor metabolites in urine and feces.

411 Amprenavir is both a substrate for and inducer of P-glycoprotein.

412 **Elimination:** Excretion of unchanged amprenavir in urine and feces is minimal.
413 Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged
414 amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single
415 dose of ¹⁴C-amprenavir can be accounted for as metabolites in urine and feces, respectively. Two
416 metabolites accounted for greater than 90% of the radiocarbon in fecal samples. The plasma
417 elimination half-life of amprenavir is approximately 7.7 hours.

418 **Special Populations: Hepatic Impairment:** The pharmacokinetics of amprenavir have
419 been studied after the administration of LEXIVA in combination with ritonavir to adult HIV-
420 1-infected patients with mild, moderate, and severe hepatic impairment. Following 2 weeks of
421 dosing with LEXIVA plus ritonavir, the AUC of amprenavir was increased by approximately
422 22% in patients with mild hepatic impairment, by approximately 70% in patients with moderate
423 hepatic impairment, and by approximately 80% in patients with severe hepatic impairment
424 compared with HIV-1-infected patients with normal hepatic function. Protein binding of
425 amprenavir was decreased in patients with hepatic impairment. The unbound fraction at 2 hours
426 (approximate C_{max}) ranged between a decrease of -7% to an increase of 57% while the unbound
427 fraction at the end of the dosing interval (C_{min}) increased from 50% to 102% [*see Dosage and*
428 *Administration (2.3)*].

429 The pharmacokinetics of amprenavir have been studied after administration of
430 amprenavir given as AGENERASE[®] Capsules to adult patients with hepatic impairment.
431 Following administration of a single 600-mg oral dose, the AUC of amprenavir was increased by
432 approximately 2.5-fold in patients with moderate cirrhosis and by approximately 4.5-fold in
433 patients with severe cirrhosis compared with healthy volunteers [*see Dosage and Administration*
434 *(2.3)*].

435 **Renal Impairment:** The impact of renal impairment on amprenavir elimination in
436 adult patients has not been studied. The renal elimination of unchanged amprenavir represents
437 approximately 1% of the administered dose; therefore, renal impairment is not expected to
438 significantly impact the elimination of amprenavir.

439 **Pediatric Patients:** The pharmacokinetics of amprenavir after administration of
440 LEXIVA Oral Suspension and LEXIVA Tablets, with or without ritonavir, have been evaluated

441 in 124 patients aged 2 to 18 years. Pharmacokinetic parameters for LEXIVA administered with
 442 food and with or without ritonavir in this patient population are provided in Tables 8 and 9
 443 below.

444

445 **Table 8. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
 446 **Parameters in Pediatric Patients Receiving LEXIVA 30 mg/kg Twice Daily**

Parameter	2 to 5 Years	
	n	LEXIVA 30 mg/kg b.i.d.
AUC ₍₂₄₎ (mcg•hr/mL)	8	31.4 (13.7, 72.4)
C _{max} (mcg/mL)	8	5.00 (1.95, 12.8)
C _{min} (mcg/mL)	17	0.454 (0.342, 0.604)

447

448 **Table 9. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
 449 **Parameters in Pediatric and Adolescent Patients Receiving LEXIVA Plus Ritonavir Twice**
 450 **Daily**

Parameter	6 to 11 Years		12 to 18 Years	
	n	LEXIVA 18 mg/kg plus Ritonavir 3 mg/kg b.i.d.	n	LEXIVA 700 mg plus Ritonavir 100 mg b.i.d.
AUC ₍₀₋₂₄₎ (mcg•hr/mL)	9	93.4 (67.8, 129)	8	58.8 (38.8, 89.0)
C _{max} (mcg/mL)	9	6.07 (4.40, 8.38)	8	4.33 (2.82, 6.65)
C _{min} (mcg/mL)	17	2.69 (2.15, 3.36)	24	1.61 (1.21, 2.15)

451

452 *Geriatric Patients:* The pharmacokinetics of amprenavir after administration of
 453 LEXIVA to patients older than 65 years have not been studied [see *Use in Specific Populations*
 454 (8.5)].

455 *Gender:* The pharmacokinetics of amprenavir after administration of LEXIVA do not
 456 differ between males and females.

457 *Race:* The pharmacokinetics of amprenavir after administration of LEXIVA do not
 458 differ between blacks and non-blacks.

459 **Drug Interactions:** [See *Contraindications (4), Warnings and Precautions (5.1), Drug*
 460 *Interactions (7).*]

461 Amprenavir, the active metabolite of fosamprenavir, is metabolized in the liver by the
 462 cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Data also suggest that
 463 amprenavir induces CYP3A4. Caution should be used when coadministering medications that

464 are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are
465 metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19,
466 CYP2E1, or uridine glucuronosyltransferase (UDPGT).

467 Drug interaction studies were performed with LEXIVA and other drugs likely to be
468 coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects
469 of coadministration on AUC, C_{\max} , and C_{\min} values are summarized in Table 10 (effect of other
470 drugs on amprenavir) and Table 12 (effect of LEXIVA on other drugs). In addition, since
471 LEXIVA delivers comparable amprenavir plasma concentrations as AGENERASE, drug
472 interaction data derived from studies with AGENERASE are provided in Tables 11 and 13. For
473 information regarding clinical recommendations, see *Drug Interactions* (7).

474

475 **Table 10. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 476 **Administration of LEXIVA in the Presence of the Coadministered Drug(s)**

Coadministered Drug(s) and Dose(s)	Dose of LEXIVA ^a	n	% Change in Amprenavir Pharmacokinetic Parameters (90% CI)		
			C _{max}	AUC	C _{min}
Antacid (MAALOX TC [®]) 30 mL single dose	1,400 mg single dose	30	↓35 (↓24 to ↓42)	↓18 (↓9 to ↓26)	↑14 (↓7 to ↑39)
Atazanavir 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	22	↔	↔	↔
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↓18 (↓34 to ↑1)	↓27 (↓41 to ↓12)	↓12 (↓27 to ↓6)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↔	↔	↔
Efavirenz 600 mg q.d. for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	↔	↓13 (↓30 to ↑7)	↓36 (↓8 to ↓56)
Efavirenz 600 mg q.d. plus additional ritonavir 100 mg q.d. for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	↑18 (↑1 to ↑38)	↑11 (0 to ↑24)	↔
Efavirenz 600 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↔	↔	↓17 (↓4 to ↓29)
Esomeprazole 20 mg q.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	25	↔	↔	↔
Esomeprazole 20 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	23	↔	↔	↔
Ethinyl estradiol/norethin- drone 0.035 mg/0.5 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir ^b 100 mg b.i.d. for 21 days	25	↔ ^c	↔ ^c	↔ ^c

Ketoconazole ^d 200 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 days	15	↔	↔	↔
Lopinavir/ritonavir 533 mg/133 mg b.i.d.	1,400 mg b.i.d. for 2 weeks	18	↓13 ^e	↓26 ^e	↓42 ^e
Lopinavir/ritonavir 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↓58 (↓42 to ↓70)	↓63 (↓51 to ↓72)	↓65 (↓54 to ↓73)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	↔ ^c	↔ ^c	↔ ^c
Nevirapine 200 mg b.i.d. for 2 weeks ^f	1,400 mg b.i.d. for 2 weeks	17	↓25 (↓37 to ↓10)	↓33 (↓45 to ↓20)	↓35 (↓50 to ↓15)
Nevirapine 200 mg b.i.d. for 2 weeks ^f	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↔	↓11 (↓23 to ↑3)	↓19 (↓32 to ↓4)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	13	↔	↑20 (↑8 to ↑34)	↑19 (↑6 to ↑33)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg b.i.d. for 14 days (fasted)	14	↓27 (↓46 to ↔)	↓36 (↓53 to ↓13)	↓43 ^g (↓59 to ↓21)
	1,400 mg b.i.d. for 14 days ^h	14	↓15 (↓27 to ↓1)	↓17 (↓27 to ↓6)	↓32 ^g (↓53 to ↓1)
	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days (fasted)	14	↓14 (↓39 to ↑20)	↓17 (↓38 to ↑12)	↓20 ^g (↓45 to ↑17)
	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days ^h	12	↓25 (↓42 to ↓2)	↓25 (↓44 to ↔)	↓33 ^g (↓52 to ↓7)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days (fasted)	13	↓18 (↓34 to ↔)	↓24 (↓41 to ↔)	↓50 ^g (↓64 to ↓31)

	1,400 mg q.d. plus ritonavir 100 mg q.d for 14 days ^h	14	↑27 (↓1 to ↑62)	↑13 (↓7 to ↑38)	↓17 ^g (↓45 to ↑26)
Ranitidine 300 mg single dose (administered 1 hour before fosamprenavir)	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	↔ (↓19 to ↑21)
Rifabutin 150 mg q.o.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↑36 ^c (↑18 to ↑55)	↑35 ^c (↑17 to ↑56)	↑17 ^c (↓1 to ↑39)
Tenofovir 300 mg q.d. for 4 to 48 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 to 48 weeks	45	NA	NA	↔ ⁱ
Tenofovir 300 mg q.d. for 4 to 48 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 4 to 48 weeks	60	NA	NA	↔ ⁱ

477 ^a Concomitant medication is also shown in this column where appropriate.

478 ^b Ritonavir C_{max}, AUC, and C_{min} increased by 63%, 45%, and 13%, respectively, compared
479 with historical control.

480 ^c Compared with historical control.

481 ^d Patients were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with
482 both ketoconazole and LEXIVA/ritonavir.

483 ^e Compared with LEXIVA 700 mg/ritonavir 100 mg b.i.d. for 2 weeks.

484 ^f Patients were receiving nevirapine for at least 12 weeks prior to study.

485 ^g C_{last} (C_{12 hr} or C_{24 hr}).

486 ^h Doses of LEXIVA and raltegravir were given with food on PK sampling days and without
487 regard to food all other days.

488 ⁱ Compared with parallel control group.

489 ↑= Increase; ↓= Decrease; ↔ = No change (↑ or ↓ less than or equal to 10%), NA = Not
490 applicable.

491

492 **Table 11. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 493 **Administration of AGENERASE in the Presence of the Coadministered Drug(s)**

Coadministered Drug(s) and Dose(s)	Dose of AGENERASE ^a	n	% Change in Amprenavir Pharmacokinetic Parameters (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir 300 mg b.i.d. for 2 to 3 weeks	900 mg b.i.d. for 2 to 3 weeks	4	↔ ^a	↔ ^a	↔ ^a
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↑40 ^b	↑130 ^b	↑125 ^b
Ethinyl estradiol/norethindrone 0.035 mg/1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
Indinavir 800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↑13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	↔	↔	NA
Methadone 44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16	↓27 ^c	↓30 ^c	↓25 ^c
Nelfinavir 750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	↔	↑189 (↑52 to ↑448)
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↔	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir 800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine 300 mg single dose	600 mg single dose	12	↔	↑13 (↓2 to ↑31)	NA

494 ^a Compared with parallel control group.

495 ^b Median percent change; confidence interval not reported.

496 ^c Compared with historical data.

497 \uparrow = Increase; \downarrow = Decrease; \leftrightarrow = No change (\uparrow or \downarrow less than 10%); NA = C_{\min} not calculated for
498 single-dose study.
499

500 **Table 12. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
 501 **Presence of Amprenavir After Administration of LEXIVA**

Coadministered Drug(s) and Dose(s)	Dose of LEXIVA ^a	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
			C _{max}	AUC	C _{min}
Atazanavir 300 mg q.d. for 10 days ^b	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	21	↓24 (↓39 to ↓6)	↓22 (↓34 to ↓9)	↔
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↑304 (↑205 to ↑437)	↑130 (↑100 to ↑164)	↓10 (↓27 to ↑12)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↑184 (↑126 to ↑257)	↑153 (↑115 to ↑199)	↑73 (↑45 to ↑108)
Esomeprazole 20 mg q.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	25	↔	↑55 (↑39 to ↑73)	ND
Esomeprazole 20 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	23	↔	↔	ND
Ethinyl estradiol ^c 0.035 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓28 (↓21 to ↓35)	↓37 (↓30 to ↓42)	ND
Ketoconazole ^d 200 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 days	15	↑25 (↑0 to ↑56)	↑169 (↑108 to ↑248)	ND
Lopinavir/ritonavir ^e 533 mg/133 mg b.i.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	18	↔ ^f	↔ ^f	↔ ^f
Lopinavir/ritonavir ^e 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↑30 (↓15 to ↑47)	↑37 (↓20 to ↑55)	↑52 (↓28 to ↑82)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	R-Methadone (active)		
			↓21 ^g (↓30 to ↓12)	↓18 ^g (↓27 to ↓8)	↓11 ^g (↓21 to ↑1)
			S-Methadone (inactive)		

			↓43 ^g (↓49 to ↓37)	↓43 ^g (↓50 to ↓36)	↓41 ^g (↓49 to ↓31)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	1,400 mg b.i.d. for 2 weeks	17	↑25 (↑14 to ↑37)	↑29 (↑19 to ↑40)	↑34 (↑20 to ↑49)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↑13 (↑3 to ↑24)	↑14 (↑5 to ↑24)	↑22 (↑9 to ↑35)
Norethindrone ^c 0.5 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓38 (↓32 to ↓44)	↓34 (↓30 to ↓37)	↓26 (↓20 to ↓32)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	14	↓20 (↓12 to ↓27)	↓22 (↓17 to ↓27)	↓29 (↓23 to ↓34)
Rifabutin 150 mg every other day for 2 weeks ⁱ (25-O-desacetylriofabutin metabolite) Rifabutin + 25-O- desacetylriofabutin metabolite	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↓14 (↓28 to ↑4) ↑579 (↑479 to ↑698) NA	↔ ↑1,120 (↑965 to ↑1,300) ↑64 (↑46 to ↑84)	↑28 (↑12 to ↑46) ↑2,510 (↑1,910 to ↑3,300) NA

502 ^a Concomitant medication is also shown in this column where appropriate.

503 ^b Comparison arm of atazanavir 300 mg q.d. plus ritonavir 100 mg q.d. for 10 days.

504 ^c Administered as a combination oral contraceptive tablet: ethinyl estradiol

505 0.035 mg/norethindrone 0.5 mg.

506 ^d Patients were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with
507 both ketoconazole and LEXIVA/ritonavir.

508 ^e Data represent lopinavir concentrations.

509 ^f Compared with lopinavir 400 mg/ritonavir 100 mg b.i.d. for 2 weeks.

510 ^g Dose normalized to methadone 100 mg. The unbound concentration of the active moiety,
511 R-methadone, was unchanged.

512 ^h Patients were receiving nevirapine for at least 12 weeks prior to study.

513 ⁱ Comparison arm of rifabutin 300 mg q.d. for 2 weeks. AUC is AUC_(0-48 hr).

514 ↑= Increase; ↓= Decrease; ↔ = No change (↑ or ↓ less than 10%); ND = Interaction cannot be
515 determined as C_{min} was below the lower limit of quantitation.

516 **Table 13. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
 517 **Presence of Amprenavir After Administration of AGENERASE**

Coadministered Drug(s) and Dose(s)	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir 300 mg b.i.d. for 2 to 3 weeks	900 mg b.i.d. for 2 to 3 weeks	4	↔ ^a	↔ ^a	↔ ^a
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↓10 (↓24 to ↑7)	↔	↔
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↓47 ^b	↓61 ^b	↓88 ^b
Ethinyl estradiol 0.035 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↔	↑32 (↓3 to ↑79)
Indinavir 800 mg t.i.d. for 2 weeks (fasted)	750 mg or 800 mg t.i.d. for 2 weeks (fasted)	9	↓22 ^a	↓38 ^a	↓27 ^a
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	↔	↔	NA
Methadone 44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16	R-Methadone (active)		
			↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
			S-Methadone (inactive)		
			↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
Nelfinavir 750 mg t.i.d. for 2 weeks (fed)	750 mg or 800 mg t.i.d. for 2 weeks (fed)	6	↑12 ^a	↑15 ^a	↑14 ^a
Norethindrone 1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↑18 (↑1 to ↑38)	↑45 (↑13 to ↑88)
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↔	↔	ND
Saquinavir 800 mg t.i.d. for 2 weeks (fed)	750 mg or 800 mg t.i.d. for 2 weeks (fed)	7	↑21 ^a	↓19 ^a	↓48 ^a

Zidovudine 300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA
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518 ^a Compared with historical data.

519 ^b Median percent change; confidence interval not reported.

520 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ less than 10%); NA = C_{min} not calculated for
521 single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit
522 of quantitation.

523

524 12.4 Microbiology

525 Mechanism of Action: Fosamprenavir is a prodrug that is rapidly hydrolyzed to
526 amprenavir by cellular phosphatases in the gut epithelium as it is absorbed. Amprenavir is an
527 inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby
528 prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the
529 formation of immature non-infectious viral particles.

530 Antiviral Activity: Fosamprenavir has little or no antiviral activity in vitro. The in vitro
531 antiviral activity of amprenavir was evaluated against HIV-1 IIB in both acutely and chronically
532 infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes.
533 The 50% effective concentration (EC₅₀) of amprenavir ranged from 0.012 to 0.08 μM in acutely
534 infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). The median
535 EC₅₀ value of amprenavir against HIV-1 isolates from clades A to G was 0.00095 μM in
536 peripheral blood mononuclear cells (PBMCs). Similarly, the EC₅₀ values for amprenavir against
537 monocytes/macrophage tropic HIV-1 isolates (clade B) ranged from 0.003 to 0.075 μM in
538 monocyte/macrophage cultures. The EC₅₀ values of amprenavir against HIV-2 isolates grown in
539 PBMCs were higher than those for HIV-1 isolates, and ranged from 0.003 to 0.11 μM.
540 Amprenavir exhibited synergistic anti-HIV-1 activity in combination with the nucleoside reverse
541 transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, stavudine, tenofovir, and
542 zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and
543 efavirenz; and the protease inhibitors atazanavir and saquinavir. Amprenavir exhibited additive
544 anti-HIV-1 activity in combination with the NNRTI nevirapine, the protease inhibitors indinavir,
545 lopinavir, nelfinavir, and ritonavir; and the fusion inhibitor enfuvirtide. These drug combinations
546 have not been adequately studied in humans.

547 Resistance: HIV-1 isolates with decreased susceptibility to amprenavir have been
548 selected in vitro and obtained from patients treated with fosamprenavir. Genotypic analysis of
549 isolates from treatment-naïve patients failing amprenavir-containing regimens showed mutations
550 in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I,
551 M46I/L, I47V, I50V, I54L/M, and I84V, as well as mutations in the p7/p1 and p1/p6 Gag and
552 Gag-Pol polyprotein precursor cleavage sites. Some of these amprenavir resistance-associated
553 mutations have also been detected in HIV-1 isolates from antiretroviral-naïve patients treated
554 with LEXIVA. Of the 488 antiretroviral-naïve patients treated with LEXIVA 1,400 mg twice
555 daily or LEXIVA 1,400 mg plus ritonavir 200 mg once daily in studies APV30001 and

556 APV30002, respectively, 61 patients (29 receiving LEXIVA and 32 receiving
 557 LEXIVA/ritonavir) with virologic failure (plasma HIV-1 RNA greater than 1,000 copies/mL on
 558 2 occasions on or after Week 12) were genotyped. Five of the 29 antiretroviral-naïve patients
 559 (17%) receiving LEXIVA without ritonavir in study APV30001 had evidence of genotypic
 560 resistance to amprenavir: I54L/M (n = 2), I54L + L33F (n = 1), V32I + I47V (n = 1), and
 561 M46I + I47V (n = 1). No amprenavir resistance-associated mutations were detected in
 562 antiretroviral-naïve patients treated with LEXIVA/ritonavir for 48 weeks in study APV30002.
 563 However, the M46I and I50V mutations were detected in isolates from 1 virologic failure patient
 564 receiving LEXIVA/ritonavir once daily at Week 160 (HIV-1 RNA greater than 500 copies/mL).
 565 Upon retrospective analysis of stored samples using an ultrasensitive assay, these resistant
 566 mutants were traced back to Week 84 (76 weeks prior to clinical virologic failure).

567 **Cross-Resistance:** Varying degrees of cross-resistance among HIV-1 protease
 568 inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1
 569 RNA level less than 400 copies/mL) and protease inhibitor-resistance mutations detected in
 570 baseline HIV-1 isolates from protease inhibitor-experienced patients receiving
 571 LEXIVA/ritonavir twice daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in study
 572 APV30003 is shown in Table 14. The majority of subjects had previously received either one
 573 (47%) or 2 protease inhibitors (36%), most commonly nelfinavir (57%) and indinavir (53%). Out
 574 of 102 subjects with baseline phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (n = 55)
 575 had resistance to at least one protease inhibitor, with 98% (n = 54) of those having resistance to
 576 nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60%
 577 (n = 58) had resistance to at least one protease inhibitor, with 97% (n = 56) of those having
 578 resistance to nelfinavir.

579

580 **Table 14. Responders at Study Week 48 by Presence of Baseline Protease Inhibitor**
 581 **Resistance-Associated Mutations^a**

Protease Inhibitor-mutations ^b	LEXIVA/Ritonavir b.i.d. (n = 88)		Lopinavir/Ritonavir b.i.d. (n = 85)	
D30N	21/22	95%	17/19	89%
N88D/S	20/22	91%	12/12	100%
L90M	16/31	52%	17/29	59%
M46I/L	11/22	50%	12/24	50%
V82A/F/T/S	2/9	22%	6/17	35%
I54V	2/11	18%	6/11	55%
I84V	1/6	17%	2/5	40%

582 ^aResults should be interpreted with caution because the subgroups were small.

583 ^bMost patients had greater than 1 protease inhibitor resistance-associated mutation at baseline.
584

585 The virologic response based upon baseline phenotype was assessed. Baseline isolates
586 from protease inhibitor-experienced patients responding to LEXIVA/ritonavir twice daily had a
587 median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of
588 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a
589 median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient
590 population, these data do not constitute definitive clinical susceptibility break points. Additional
591 data are needed to determine clinically relevant break points for LEXIVA.

592 Isolates from 15 of the 20 patients receiving twice-daily LEXIVA/ritonavir up to
593 Week 48 and experiencing virologic failure/ongoing replication were subjected to genotypic
594 analysis. The following amprenavir resistance-associated mutations were found either alone or in
595 combination: V32I, M46I/L, I47V, I50V, I54L/M, and I84V. Isolates from 4 of the 16 patients
596 continuing to receive twice-daily LEXIVA/ritonavir up to Week 96 who experienced virologic
597 failure underwent genotypic analysis. Isolates from 2 patients contained amprenavir
598 resistance-associated mutations: V32I, M46I, and I47V in 1 isolate and I84V in the other.

599 **13 NONCLINICAL TOXICOLOGY**

600 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

601 In long-term carcinogenicity studies, fosamprenavir was administered orally for up to
602 104 weeks at doses of 250, 400, or 600 mg/kg/day in mice and at doses of 300, 825, or
603 2,250 mg/kg/day in rats. Exposures at these doses were 0.3- to 0.7-fold (mice) and 0.7- to
604 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to
605 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of
606 fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were
607 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir
608 plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and
609 hepatocellular carcinomas at all doses in male mice and at 600 mg/kg/day in female mice, and in
610 hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and at
611 835 mg/kg/day and 2,250 mg/kg/day in female rats. The relevance of the hepatocellular findings
612 in the rodents for humans is uncertain. Repeat dose studies with fosamprenavir in rats produced
613 effects consistent with enzyme induction, which predisposes rats, but not humans, to thyroid
614 neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at
615 825 mg/kg/day and 2,250 mg/kg/day, and an increase in uterine endometrial adenocarcinoma at
616 2,250 mg/kg/day. The incidence of endometrial findings was slightly increased over concurrent
617 controls, but was within background range for female rats. The relevance of the uterine
618 endometrial adenocarcinoma findings in rats for humans is uncertain.

619 Fosamprenavir was not mutagenic or genotoxic in a battery of in vitro and in vivo assays.
620 These assays included bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus,
621 and chromosome aberrations in human lymphocytes.

622 The effects of fosamprenavir on fertility and general reproductive performance were
623 investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks
624 before mating through postpartum day 6). Systemic exposures ($AUC_{0-24 \text{ hr}}$) to amprenavir in
625 these studies were 3 (males) to 4 (females) times higher than exposures in humans following
626 administration of the MRHD of fosamprenavir alone or similar to those seen in humans
627 following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not
628 impair mating or fertility of male or female rats and did not affect the development and
629 maturation of sperm from treated rats.

630 **14 CLINICAL STUDIES**

631 **14.1 Therapy-Naive Adult Patients**

632 Study APV30001: APV30001 was a randomized, open-label study, comparing
633 treatment with LEXIVA Tablets (1,400 mg twice daily) versus nelfinavir (1,250 mg twice daily)
634 in 249 antiretroviral treatment-naive patients. Both groups of patients also received abacavir
635 (300 mg twice daily) and lamivudine (150 mg twice daily).

636 The mean age of the patients in this study was 37 years (range: 17 to 70 years), 69% of
637 the patients were males, 20% were CDC Class C (AIDS), 24% were Caucasian, 32% were black,
638 and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells/mm³ (range: 2 to
639 1,136 cells/mm³; 18% of patients had a CD4+ cell count of less than 50 cells/mm³ and 30% were
640 in the range of 50 to less than 200 cells/mm³). Baseline median HIV-1 RNA was
641 4.83 log₁₀ copies/mL (range: 1.69 to 7.41 log₁₀ copies/mL; 45% of patients had greater than
642 100,000 copies/mL).

643 The outcomes of randomized treatment are provided in Table 15.

644

645 **Table 15. Outcomes of Randomized Treatment Through Week 48 (APV30001)**

Outcome (Rebound or discontinuation = failure)	LEXIVA 1,400 mg b.i.d. (n = 166)	Nelfinavir 1,250 mg b.i.d. (n = 83)
Responder ^a	66% (57%)	52% (42%)
Virologic failure	19%	32%
Rebound	16%	19%
Never suppressed through Week 48	3%	13%
Clinical progression	1%	1%
Death	0%	1%
Discontinued due to adverse reactions	4%	2%
Discontinued due to other reasons ^b	10%	10%

646 ^a Patients achieved and maintained confirmed HIV-1 RNA less than 400 copies/mL (less than
647 50 copies/mL) through Week 48 (Roche AMPLICOR HIV-1 MONITOR Assay Version 1.5).

648 ^b Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,
649 and other reasons.

650

651 Treatment response by viral load strata is shown in Table 16.

652

653 **Table 16. Proportions of Responders Through Week 48 by Screening Viral Load**
654 **(APV30001)**

Screening Viral Load HIV-1 RNA (copies/mL)	LEXIVA 1,400 mg b.i.d.		Nelfinavir 1,250 mg b.i.d.	
	<400 copies/mL	n	<400 copies/mL	n
≤100,000	65%	93	65%	46
>100,000	67%	73	36%	37

655

656 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
657 were 201 cells/mm³ in the group receiving LEXIVA and 216 cells/mm³ in the nelfinavir group.

658 **Study APV30002:** APV30002 was a randomized, open-label study, comparing
659 treatment with LEXIVA Tablets (1,400 mg once daily) plus ritonavir (200 mg once daily) versus
660 nelfinavir (1,250 mg twice daily) in 649 treatment-naive patients. Both treatment groups also
661 received abacavir (300 mg twice daily) and lamivudine (150 mg twice daily).

662 The mean age of the patients in this study was 37 years (range: 18 to 69 years), 73% of
663 the patients were males, 22% were CDC Class C, 53% were Caucasian, 36% were black, and 8%
664 were Hispanic. At baseline, the median CD4+ cell count was 170 cells/mm³ (range: 1 to
665 1,055 cells/mm³; 20% of patients had a CD4+ cell count of less than 50 cells/mm³ and 35% were
666 in the range of 50 to less than 200 cells/mm³). Baseline median HIV-1 RNA was
667 4.81 log₁₀ copies/mL (range: 2.65 to 7.29 log₁₀ copies/mL; 43% of patients had greater than
668 100,000 copies/mL).

669 The outcomes of randomized treatment are provided in Table 17.

670

671 **Table 17. Outcomes of Randomized Treatment Through Week 48 (APV30002)**

Outcome (Rebound or discontinuation = failure)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d. (n = 322)	Nelfinavir 1,250 mg b.i.d. (n = 327)
Responder ^a	69% (58%)	68% (55%)
Virologic failure	6%	16%
Rebound	5%	8%
Never suppressed through Week 48	1%	8%
Death	1%	0%
Discontinued due to adverse reactions	9%	6%
Discontinued due to other reasons ^b	15%	10%

672 ^a Patients achieved and maintained confirmed HIV-1 RNA less than 400 copies/mL (less than
673 50 copies/mL) through Week 48 (Roche AMPLICOR HIV-1 MONITOR Assay Version 1.5).

674 ^b Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,
675 and other reasons.

676

677 Treatment response by viral load strata is shown in Table 18.

678

679 **Table 18. Proportions of Responders Through Week 48 by Screening Viral Load**
680 **(APV30002)**

Screening Viral Load HIV-1 RNA (copies/mL)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d.		Nelfinavir 1,250 mg b.i.d.	
	<400 copies/mL	n	<400 copies/mL	n
≤100,000	72%	197	73%	194
>100,000	66%	125	64%	133

681

682 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
683 were 203 cells/mm³ in the group receiving LEXIVA and 207 cells/mm³ in the nelfinavir group.

684 **14.2 Protease Inhibitor-Experienced Adult Patients**

685 Study APV30003: APV30003 was a randomized, open-label, multicenter study
686 comparing 2 different regimens of LEXIVA plus ritonavir (LEXIVA Tablets 700 mg twice daily
687 plus ritonavir 100 mg twice daily or LEXIVA Tablets 1,400 mg once daily plus ritonavir 200 mg
688 once daily) versus lopinavir/ritonavir (400 mg/100 mg twice daily) in 315 patients who had
689 experienced virologic failure to 1 or 2 prior protease inhibitor-containing regimens.

690 The mean age of the patients in this study was 42 years (range: 24 to 72 years), 85% were
691 male, 33% were CDC Class C, 67% were Caucasian, 24% were black, and 9% were Hispanic.

692 The median CD4+ cell count at baseline was 263 cells/mm³ (range: 2 to 1,171 cells/mm³).

693 Baseline median plasma HIV-1 RNA level was 4.14 log₁₀ copies/mL (range: 1.69 to
694 6.41 log₁₀ copies/mL).

695 The median durations of prior exposure to NRTIs were 257 weeks for patients receiving
696 LEXIVA/ritonavir twice daily (79% had greater than or equal to 3 prior NRTIs) and 210 weeks
697 for patients receiving lopinavir/ritonavir (64% had greater than or equal to 3 prior NRTIs). The
698 median durations of prior exposure to protease inhibitors were 149 weeks for patients receiving
699 LEXIVA/ritonavir twice daily (49% received greater than or equal to 2 prior protease inhibitors)
700 and 130 weeks for patients receiving lopinavir/ritonavir (40% received greater than or equal to
701 2 prior protease inhibitors).

702 The time-averaged changes in plasma HIV-1 RNA from baseline (AAUCMB) at
703 48 weeks (the endpoint on which the study was powered) were -1.4 log₁₀ copies/mL for
704 twice-daily LEXIVA/ritonavir and -1.67 log₁₀ copies/mL for the lopinavir/ritonavir group.

705 The proportions of patients who achieved and maintained confirmed HIV-1 RNA less
706 than 400 copies/mL (secondary efficacy endpoint) were 58% with twice-daily LEXIVA/ritonavir
707 and 61% with lopinavir/ritonavir (95% CI for the difference: -16.6, 10.1). The proportions of
708 patients with HIV-1 RNA less than 50 copies/mL with twice-daily LEXIVA/ritonavir and with
709 lopinavir/ritonavir were 46% and 50%, respectively (95% CI for the difference: -18.3, 8.9). The
710 proportions of patients who were virologic failures were 29% with twice-daily
711 LEXIVA/ritonavir and 27% with lopinavir/ritonavir.

712 The frequency of discontinuations due to adverse events and other reasons, and deaths
713 were similar between treatment arms.

714 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
715 were 81 cells/mm³ with twice-daily LEXIVA/ritonavir and 91 cells/mm³ with lopinavir/ritonavir.

716 This study was not large enough to reach a definitive conclusion that LEXIVA/ritonavir
717 and lopinavir/ritonavir are clinically equivalent.

718 Once-daily administration of LEXIVA plus ritonavir is not recommended for protease
719 inhibitor-experienced patients. Through Week 48, 50% and 37% of patients receiving LEXIVA
720 1,400 mg plus ritonavir 200 mg once daily had plasma HIV-1 RNA less than 400 copies/mL and
721 less than 50 copies/mL, respectively.

722 **14.3 Pediatric Patients**

723 Two open-label studies in pediatric patients aged 2 to 18 years were conducted. In one
724 study, twice-daily dosing regimens (LEXIVA with or without ritonavir) were evaluated in
725 combination with other antiretroviral agents. A second study evaluated once-daily dosing of
726 LEXIVA with ritonavir; the data from this study were insufficient to support a once-daily dosing
727 regimen in any pediatric patient population.

728 LEXIVA: Eighteen (16 therapy-naive and 2 therapy-experienced) pediatric patients
729 received LEXIVA Oral Suspension without ritonavir twice daily. At Week 24, 67% (12/18)
730 achieved HIV-1 RNA less than 400 copies/mL, and the median increase from baseline in CD4+
731 cell count was 353 cells/mm³.

732 LEXIVA plus ritonavir: Twenty-seven protease inhibitor-naive and 30 protease
733 inhibitor-experienced pediatric patients received LEXIVA Oral Suspension or Tablets with
734 ritonavir twice daily. At Week 24, 70% of protease inhibitor-naive (19/27) and 57% of protease
735 inhibitor-experienced (17/30) patients achieved HIV-1 RNA less than 400 copies/mL; median
736 increases from baseline in CD4+ cell counts were 131 cells/mm³ and 149 cells/mm³ in protease
737 inhibitor-naive and experienced patients, respectively.

738 **16 HOW SUPPLIED/STORAGE AND HANDLING**

739 LEXIVA Tablets, 700 mg, are pink, film-coated, capsule-shaped, biconvex tablets, with
740 “GX LL7” debossed on one face.

741 Bottle of 60 with child-resistant closure (NDC 49702-207-18).

742 Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C
743 (59° to 86°F) (see USP Controlled Room Temperature). Keep container tightly closed.

744 LEXIVA Oral Suspension, a white to off-white grape-bubblegum-peppermint-flavored
745 suspension, contains 50 mg of fosamprenavir as fosamprenavir calcium equivalent to
746 approximately 43 mg of amprenavir in each 1 mL.

747 Bottle of 225 mL with child-resistant closure (NDC 49702-208-53).

748 This product does not require reconstitution.

749 Store at 5° to 30°C (41° to 86°F). Shake vigorously before using. Do not freeze.

750 **17 PATIENT COUNSELING INFORMATION**

751 *See FDA-approved Patient Labeling (Patient Information).*

752 **17.1 Drug Interactions**

753 A statement to patients and healthcare providers is included on the product's bottle label:
754 **ALERT:** Find out about medicines that should NOT be taken with LEXIVA.

755 LEXIVA may interact with many drugs; therefore, patients should be advised to report to
756 their healthcare provider the use of any other prescription or nonprescription medication or
757 herbal products, particularly St. John's wort.

758 Patients receiving PDE5 inhibitors should be advised that they may be at an increased
759 risk of PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and
760 priapism, and should promptly report any symptoms to their healthcare provider.

761 Patients receiving hormonal contraceptives should be instructed to use alternate
762 contraceptive measures during therapy with LEXIVA because hormonal levels may be altered,
763 and if used in combination with LEXIVA and ritonavir, liver enzyme elevations may occur.

764 **17.2 Sulfa Allergy**

765 Patients should inform their healthcare provider if they have a sulfa allergy. The potential
766 for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown.

767 **17.3 Redistribution/Accumulation of Body Fat**

768 Patients should be informed that redistribution or accumulation of body fat may occur in
769 patients receiving antiretroviral therapy, including LEXIVA, and that the cause and long-term
770 health effects of these conditions are not known at this time.

771 **17.4 Information About Therapy With LEXIVA**

772 Patients should be informed that LEXIVA is not a cure for HIV infection and that they
773 may continue to develop opportunistic infections and other complications associated with HIV
774 disease. The long-term effects of LEXIVA are unknown at this time. Patients should be told that
775 there are currently no data demonstrating that therapy with LEXIVA can reduce the risk of
776 transmitting HIV to others.

777 Patients should be told that sustained decreases in plasma HIV-1 RNA have been
778 associated with a reduced risk of progression to AIDS and death. Patients should remain under
779 the care of a physician while using LEXIVA. Patients should be advised to take LEXIVA every
780 day as prescribed. LEXIVA must always be used in combination with other antiretroviral drugs.
781 Patients should not alter the dose or discontinue therapy without consulting their physician. If a
782 dose is missed, patients should take the dose as soon as possible and then return to their normal
783 schedule. However, if a dose is skipped, the patient should not double the next dose.

784 **17.5 Oral Suspension**

785 Patients should be instructed to shake the bottle vigorously before each use and that
786 refrigeration of the oral suspension may improve the taste for some patients.

787

788 LEXIVA and AGENERASE are registered trademarks of ViiV Healthcare.

789

790 The brands listed are trademarks of their respective owners and are not trademarks of ViiV
791 Healthcare. The makers of these brands are not affiliated with and do not endorse ViiV
792 Healthcare or its products.

793

794

795 Manufactured for:



ViiV Healthcare

Research Triangle Park, NC 27709



Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

796

797 by:



GlaxoSmithKline

798

799 GlaxoSmithKline

800 Research Triangle Park, NC 27709

801

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804 May 2011

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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PATIENT INFORMATION

LEXIVA[®]
(lex-EE-vah)
(fosamprenavir calcium)
Tablets and Oral Suspension

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822

Read the Patient Information that comes with LEXIVA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. It is important to remain under a healthcare provider's care while taking LEXIVA. Do not change or stop treatment without first talking with your healthcare provider. Talk to your healthcare provider or pharmacist if you have any questions about LEXIVA.

823
824

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

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826
827

LEXIVA can cause dangerous and life-threatening interactions if taken with certain other medicines. Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

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829
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- Some medicines cannot be taken at all with LEXIVA.
- Some medicines will require dose changes if taken with LEXIVA.
- Some medicines will require close monitoring if you take them with LEXIVA.

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Know all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Keep a list of the medicines you take. Show this list to all your healthcare providers and pharmacists anytime you get a new medicine or refill. Your healthcare providers and pharmacists must know all the medicines you take. They will tell you if you can take other medicines with LEXIVA. Do not start any new medicines while you are taking LEXIVA without talking with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for a list of medicines that can interact with LEXIVA.

839
840

What is LEXIVA?

841
842
843
844

LEXIVA is a medicine you take by mouth to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome). LEXIVA belongs to a class of anti-HIV medicines called protease inhibitors. LEXIVA is always used with other anti-HIV medicines. When used in combination therapy, LEXIVA may help lower the amount of HIV found in your

845 blood, raise CD4+ (T) cell counts, and keep your immune system as healthy as possible, so it can
846 help fight infection. However, LEXIVA does not work in all patients with HIV.

847

848 **LEXIVA does not:**

- 849 • cure HIV infection or AIDS. We do not know if LEXIVA will help you live longer or have
850 fewer of the medical problems (opportunistic infections) that people get with HIV or AIDS.
851 Opportunistic infections are infections that develop because the immune system is weak.
852 Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium*
853 complex (MAC) infections. It is very important that you see your healthcare provider
854 regularly while you are taking LEXIVA. The long-term effects of LEXIVA are not known.
- 855 • lower the risk of passing HIV to other people through sexual contact, sharing needles, or
856 being exposed to your blood. For your health and the health of others, it is important to
857 always practice safer sex by using a latex or polyurethane condom to lower the chance of
858 sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

859

860 LEXIVA has not been fully studied in children younger than 2 years or in adults older than 65.

861

862 **Who should not take LEXIVA?**

863 **Do not take LEXIVA if you:**

- 864 • are taking certain other medicines. Read the section “What is the most important information I
865 should know about LEXIVA?” Do not take the following medicines* with LEXIVA. You
866 could develop serious or life-threatening problems.
 - 867 • HALCION® (triazolam; used for insomnia)
 - 868 • Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine
869 such as CAFERGOT®, MIGRANAL®, D.H.E. 45®, ergotrate maleate, METHERGINE®,
870 and others (used for migraine headaches)
 - 871 • PROPULSID® (cisapride), used for certain stomach problems
 - 872 • VERSED® (midazolam), used for sedation
 - 873 • ORAP® (pimozide), used for Tourette’s disorder
 - 874 • REVATIO® (sildenafil), used for treatment of pulmonary arterial hypertension
 - 875 • UROXATRAL® (alfuzosin), used for benign prostatic hyperplasia (BPH)
- 876 • are allergic to LEXIVA or any of its ingredients. The active ingredient is fosamprenavir
877 calcium. See the end of this leaflet for a list of all the ingredients in LEXIVA.
- 878 • are allergic to AGENERASE (amprenavir).

879

880 You should not take AGENERASE (amprenavir) and LEXIVA at the same time.

881

882 There are other medicines you should not take if you are taking LEXIVA and NORVIR®
883 (ritonavir) together. You could develop serious or life-threatening problems. Tell your healthcare

884 provider about all medicines you are taking before you begin taking LEXIVA and NORVIR
885 (ritonavir) together.

886

887 **What should I tell my healthcare provider before taking LEXIVA?**

888 Before taking LEXIVA, tell your healthcare provider about all of your medical conditions
889 including if you:

- 890 • are pregnant or planning to become pregnant. It is not known if LEXIVA can harm your
891 unborn baby. You and your healthcare provider will need to decide if LEXIVA is right for
892 you. If you use LEXIVA while you are pregnant, talk to your healthcare provider about how
893 you can be on the Antiretroviral Pregnancy Registry.
- 894 • are breastfeeding. You should not breastfeed if you are HIV-positive because of the chance of
895 passing the HIV virus to your baby through your milk. Also, it is not known if LEXIVA can
896 pass into your breast milk and if it can harm your baby. If you are a woman who has or will
897 have a baby, talk with your healthcare provider about the best way to feed your baby.
- 898 • have liver problems. You may be given a lower dose of LEXIVA or LEXIVA may not be
899 right for you.
- 900 • have kidney problems
- 901 • have diabetes. You may need dose changes in your insulin or other diabetes medicines.
- 902 • have hemophilia
- 903 • are allergic to sulfa medicines

904

905 Before taking LEXIVA, tell your healthcare provider about all the medicines you take, including
906 prescription and nonprescription medicines, vitamins, and herbal supplements. LEXIVA can
907 cause dangerous and life-threatening interactions if taken with certain other medicines. You may
908 need dose changes in some of your medicines or closer monitoring with some medicines if you
909 also take LEXIVA (see “What is the most important information I should know about
910 LEXIVA.”). Know all the medicines that you take and keep a list of them with you to show
911 healthcare providers and pharmacists.

912

913 Women who use birth control pills should choose a different kind of contraception. The use of
914 LEXIVA with NORVIR (ritonavir) in combination with birth control pills may be harmful to
915 your liver. The use of LEXIVA with or without NORVIR may decrease the effectiveness of birth
916 control pills. Talk to your healthcare provider about choosing an effective contraceptive.

917

918 **How should I take LEXIVA?**

- 919 • Take LEXIVA exactly as your healthcare provider prescribed.
- 920 • Do not take more or less than your prescribed dose of LEXIVA at any one time. Do not
921 change your dose or stop taking LEXIVA without talking with your healthcare provider.
- 922 • You can take LEXIVA Tablets with or without food.
- 923 • Adults should take LEXIVA Oral Suspension without food.

- 924 • Pediatric patients should take LEXIVA Oral Suspension with food. If vomiting occurs within
925 30 minutes after dosing, the dose should be repeated.
- 926 • Shake LEXIVA Oral Suspension vigorously before each use.
- 927 • When your supply of LEXIVA or other anti-HIV medicine starts to run low, get more from
928 your healthcare provider or pharmacy. The amount of HIV virus in your blood may increase if
929 one or more of the medicines are stopped, even for a short time.
- 930 • Stay under the care of a healthcare provider while using LEXIVA.
- 931 • It is important that you do not miss any doses. If you miss a dose of LEXIVA by more than
932 4 hours, wait and take the next dose at the regular time. However, if you miss a dose by fewer
933 than 4 hours, take your missed dose right away. Then take your next dose at the regular time.
- 934 • If you take too much LEXIVA, call your healthcare provider or poison control center right
935 away.

936

937 **What should I avoid while taking LEXIVA?**

- 938 • Do not use certain medicines while you are taking LEXIVA. See “What is the most important
939 information I should know about LEXIVA” and “Who should not take LEXIVA?”
- 940 • Do not breastfeed. See “Before taking LEXIVA, tell your healthcare provider”. Talk with
941 your healthcare provider about the best way to feed your baby.
- 942 • Avoid doing things that can spread HIV infection since LEXIVA doesn't stop you from
943 passing the HIV infection to others.
- 944 • Do not share needles or other injection equipment.
- 945 • Do not share personal items that can have blood or body fluids on them, like toothbrushes or
946 razor blades.
- 947 • Do not have any kind of sex without protection. Always practice safer sex by using a latex or
948 polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or
949 blood.

950

951 **What are the possible side effects of LEXIVA?**

952 LEXIVA may cause the following side effects:

- 953 • skin rash. Skin rashes, some with itching, have happened in patients taking LEXIVA.
954 Swelling of the face, lips, and tongue (angioedema) has also been reported. Tell your
955 healthcare provider if you get a rash or develop facial swelling after starting LEXIVA.
- 956 • diabetes and high blood sugar (hyperglycemia). Some patients had diabetes before taking
957 LEXIVA while others did not. Some patients may need changes in their diabetes medicine.
958 Others may need a new diabetes medicine.
- 959 • increased bleeding problems in some patients with hemophilia.
- 960 • worse liver disease. Patients with liver problems, including hepatitis B or C, are more likely to
961 get worse liver disease when they take anti-HIV medicines like LEXIVA.
- 962 • changes in blood tests. Some people have changes in blood tests while taking LEXIVA. These
963 include increases seen in liver function tests and blood fat levels, and decreases in white blood

964 cells. Your healthcare provider may do regular blood tests to see if LEXIVA is affecting your
965 body.

- 966 • changes in body fat. These changes have happened in patients taking antiretroviral medicines
967 like LEXIVA. The changes may include an increased amount of fat in the upper back and
968 neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face
969 may also happen. The cause and long-term health effects of these conditions are not known at
970 this time.
- 971 • kidney stones have been reported in some patients taking LEXIVA. If you develop signs or
972 symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) tell
973 your healthcare provider right away.

974

975 Common side effects of LEXIVA are nausea, vomiting, and diarrhea. Tell your healthcare
976 provider about any side effects that bother you or that won't go away.

977

978 This list of side effects of LEXIVA is not complete. Call your doctor for medical advice about
979 side effects. You may report side effects to FDA at 1-800-FDA-1088.

980

981 **How should I store LEXIVA?**

- 982 • LEXIVA Tablets should be stored at room temperature between 59° and 86°F (15° to 30°C).
983 Keep the container of LEXIVA Tablets tightly closed.
- 984 • LEXIVA Oral Suspension may be stored at room temperature or refrigerated. Refrigeration of
985 LEXIVA Oral Suspension may improve taste for some patients. Do not freeze.
- 986 • Keep LEXIVA and all medicines out of the reach of children.
- 987 • Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw
988 any medicine away, it is out of the reach of children.

989

990 **General information about LEXIVA**

991 Medicines are sometimes prescribed for conditions that are not mentioned in patient information
992 leaflets. Do not use LEXIVA for a condition for which it was not prescribed. Do not give
993 LEXIVA to other people, even if they have the same symptoms you have. It may harm them.

994

995 This leaflet summarizes the most important information about LEXIVA. If you would like more
996 information, talk with your healthcare provider. You can ask your pharmacist or healthcare
997 provider for information about LEXIVA that is written for health professionals. For more
998 information you can call toll-free 877-844-8872 or visit www.LEXIVA.com.

999

1000 **What are the ingredients in LEXIVA?**

1001 Tablets:

1002 Active Ingredient: fosamprenavir calcium.

1003 Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate,
1004 microcrystalline cellulose, and povidone K30. The tablet film-coating contains the inactive
1005 ingredients hypromellose, iron oxide red, titanium dioxide, and triacetin.

1006
1007 LEXIVA Tablets, 700 mg, are pink in color and are capsule-shaped, with the letters “GX LL7”
1008 printed on one side of the tablet.



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1011 Oral Suspension:

1012 Active Ingredient: fosamprenavir calcium

1013 Inactive ingredients: artificial grape-bubblegum flavor, calcium chloride dihydrate,
1014 hypromellose, methylparaben, natural peppermint flavor, polysorbate 80, propylene glycol,
1015 propylparaben, purified water, and sucralose.

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1020 Healthcare. The makers of these brands are not affiliated with and do not endorse ViiV
1021 Healthcare or its products.

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1023

1024 Manufactured for:



ViiV Healthcare

Research Triangle Park, NC 27709



Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

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1026



GlaxoSmithKline

1027 by:

1028 GlaxoSmithKline

1029 Research Triangle Park, NC 27709

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