

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

RECENT MAJOR CHANGES

Dosage and Administration, Patients With Hepatic Impairment (2.3) 4/2009

Warnings and Precautions (5.8) 9/2009

Warnings and Precautions, Nephrolithiasis (5.11) 9/2009

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 $\geq 4\%$) 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 GlaxoSmithKline at 1-888-825-5249 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: September 2009

LXV:10PI

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Adults
- 2.2 Pediatric Patients (2 to 18 years of age)
- 2.3 Patients With Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Drug Interactions
- 5.2 Skin Reactions
- 5.3 Sulfa Allergy
- 5.4 Hepatic Toxicity
- 5.5 Diabetes/Hyperglycemia
- 5.6 Immune Reconstitution Syndrome
- 5.7 Fat Redistribution
- 5.8 Lipid Elevations
- 5.9 Hemolytic Anemia
- 5.10 Patients With Hemophilia
- 5.11 Nephrolithiasis
- 5.12 Resistance/Cross-Resistance

6 ADVERSE REACTIONS

- 6.1 Clinical Trials
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 CYP Inhibitors and Inducers
- 7.2 Drugs That Should Not Be Coadministered With LEXIVA

7.3 Established and Other Potentially Significant Drug Interactions

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Therapy-Naive Adult Patients
- 14.2 Protease Inhibitor-Experienced Adult Patients
- 14.3 Pediatric Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Drug Interactions
- 17.2 Sulfa Allergy
- 17.3 Redistribution/Accumulation of Body Fat
- 17.4 Information About Therapy With LEXIVA
- 17.5 Oral Suspension

*Sections or subsections omitted from the full prescribing information are not listed.

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 (2 to 18 years of age)**

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

38 Therapy-Naive 2 to 5 Years of Age:

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

41 Therapy-Naive ≥6 Years of Age:

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

46 Therapy-Experienced ≥6 Years of Age:

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

49 Other Dosing Considerations:

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

55 **2.3 Patients With Hepatic Impairment**

56 *See Clinical Pharmacology (12.3).*

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

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

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

69 **3 DOSAGE FORMS AND STRENGTHS**

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

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

74 **4 CONTRAINDICATIONS**

75 LEXIVA is contraindicated:

- 76 • in patients with previously demonstrated clinically significant hypersensitivity (e.g.,
77 Stevens-Johnson syndrome) to any of the components of this product or to amprenavir.

- 78 • when coadministered with drugs that are highly dependent on CYP3A4 for clearance and for
 79 which elevated plasma concentrations are associated with serious and/or life-threatening
 80 events (Table 1).

81
 82

Table 1. Drugs Contraindicated With LEXIVA

Drug Class/Drug Name	Clinical Comment
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.
Sedative/hypnotics: Midazolam, triazolam	POTENTIAL for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

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

84

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

88 **5 WARNINGS AND PRECAUTIONS**

89 **5.1 Drug Interactions**

90 See Table 1 for listings of drugs that are contraindicated due to potentially
91 life-threatening adverse events, significant drug interactions, or due to loss of virologic activity
92 [see *Contraindications (4)*, *Drug Interactions (7.2)*].

93 **5.2 Skin Reactions**

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

98 **5.3 Sulfa Allergy**

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

107 **5.4 Hepatic Toxicity**

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

114 **5.5 Diabetes/Hyperglycemia**

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

123 **5.6 Immune Reconstitution Syndrome**

124 Immune reconstitution syndrome has been reported in patients treated with combination
125 antiretroviral therapy, including LEXIVA. During the initial phase of combination antiretroviral
126 treatment, patients whose immune system responds may develop an inflammatory response to
127 indolent or residual opportunistic infections (such as *Mycobacterium avium* infection,

128 cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may
129 necessitate further evaluation and treatment.

130 **5.7 Fat Redistribution**

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

136 **5.8 Lipid Elevations**

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

141 **5.9 Hemolytic Anemia**

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

143 **5.10 Patients With Hemophilia**

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

148 **5.11 Nephrolithiasis**

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

153 **5.12 Resistance/Cross-Resistance**

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

158 **6 ADVERSE REACTIONS**

- 159 • Severe or life-threatening skin reactions have been reported with the use of LEXIVA [*see*
160 *Warnings and Precautions (5.2)*].
- 161 • The most common moderate to severe adverse reactions in clinical studies of LEXIVA were
162 diarrhea, rash, nausea, vomiting, and headache.
- 163 • Treatment discontinuation due to adverse events occurred in 6.4% of patients receiving
164 LEXIVA and in 5.9% of patients receiving comparator treatments. The most common adverse
165 reactions leading to discontinuation of LEXIVA (incidence \leq 1% of patients) included
166 diarrhea, nausea, vomiting, AST increased, ALT increased, and rash.

167 **6.1 Clinical Trials**

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

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

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

181
 182 **Table 2. Selected Moderate/Severe Clinical Adverse Reactions Reported in ≥2% of**
 183 **Antiretroviral-Naïve 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%

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

185

186 **Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in $\geq 2\%$ of**
 187 **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%

188 ^aAll patients also received 2 reverse transcriptase inhibitors.

189
 190 Skin rash (without regard to causality) occurred in approximately 19% of patients treated
 191 with LEXIVA in the pivotal efficacy studies. Rashes were usually maculopapular and of mild or
 192 moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of
 193 LEXIVA and had a median duration of 13 days. Skin rash led to discontinuation of LEXIVA in
 194 <1% of patients. In some patients with mild or moderate rash, dosing with LEXIVA was often
 195 continued without interruption; if interrupted, reintroduction of LEXIVA generally did not result
 196 in rash recurrence.

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

199

200 **Table 4. Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Antiretroviral-Naive**
 201 **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%

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

203 ^bFasting specimens.

204 ULN = Upper limit of normal.

205

206 The incidence of Grade 3 or 4 hyperglycemia in antiretroviral-naive patients who
 207 received LEXIVA in the pivotal studies was <1%.

208

209 **Table 5. Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Protease**
 210 **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

211 ^aAll patients also received 2 reverse transcriptase inhibitors.

212 ^bFasting specimens.

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

214 ULN = Upper limit of normal.

215

216 Pediatric Patients: LEXIVA with and without ritonavir was studied in 144 pediatric
 217 patients 2 to 18 years of age in 2 open-label studies. Safety information from 75 pediatric
 218 patients receiving LEXIVA twice daily with or without ritonavir follows.

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

228 **6.2 Postmarketing Experience**

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

234 Cardiac Disorders: Myocardial infarction.

235 Metabolism and Nutrition Disorders: Hypercholesterolemia.

236 Nervous System Disorders: Oral paresthesia.

237 Skin and Subcutaneous Tissue Disorders: Angioedema.

238 Urogenital: Nephrolithiasis.

239 **7 DRUG INTERACTIONS**

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

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

243 **7.1 CYP Inhibitors and Inducers**

244 Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of cytochrome P450
245 3A4 metabolism and therefore should not be administered concurrently with medications with
246 narrow therapeutic windows that are substrates of CYP3A4. Data also suggest that amprenavir
247 induces CYP3A4.

248 Amprenavir is metabolized by CYP3A4. Coadministration of LEXIVA and drugs that
249 induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its
250 therapeutic effect. Coadministration of LEXIVA and drugs that inhibit CYP3A4 may increase
251 amprenavir concentrations and increase the incidence of adverse effects.

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

258 There are other agents that may result in serious and/or life-threatening drug interactions
259 *[see Contraindications (4)].*
260 **7.2 Drugs That Should Not Be Coadministered With LEXIVA**
261 *See Contraindications (4).*

262 **7.3 Established and Other Potentially Significant Drug Interactions**

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

266
 267 **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.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.

	LEXIVA/ritonavir: ↓Atazanavir ↔Amprenavir	
HIV protease inhibitors: Indinavir ^a , nelfinavir ^a	LEXIVA: ↑Amprenavir Effect on indinavir and nelfinavir is not well established. LEXIVA/ritonavir: Interaction has not been evaluated.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Lopinavir/ritonavir ^a	↓Amprenavir ↓Lopinavir	An increased rate of adverse events has been observed. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Saquinavir ^a	LEXIVA: ↓Amprenavir Effect on saquinavir is not well established. LEXIVA/ritonavir: Interaction has not been evaluated.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
<i>Other Agents</i>		
Antiarrhythmics: Amiodarone, bepridil, lidocaine (systemic), and quinidine	↑Antiarrhythmics	Use with caution. Increased exposure may be associated with life-threatening reactions such as cardiac arrhythmias. Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.

<p>Anticonvulsants: Carbamazepine, phenobarbital, phenytoin</p> <p>Phenytoin^a</p>	<p>LEXIVA: ↓Amprenavir</p> <p>LEXIVA/ritonavir: ↑Amprenavir ↓Phenytoin</p>	<p>Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.</p> <p>Plasma phenytoin concentrations should be monitored and phenytoin dose should be increased as appropriate. No change in LEXIVA/ritonavir dose is recommended.</p>
<p>Antidepressant: Paroxetine, trazodone</p>	<p>↓Paroxetine</p> <p>↑Trazodone</p>	<p>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).</p> <p>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>

<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 (>200 mg/day) are not recommended.</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. LEXIVA: A dosage reduction of rifabutin by at least half the recommended dose is required. 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, nifedipine, 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>Histamine H₂-receptor</p>	<p>LEXIVA:</p>	<p>Use with caution. LEXIVA may be</p>

<p>antagonists: Cimetidine, famotidine, nizatidine, ranitidine^a</p>	<p>↓Amprenavir</p> <p>LEXIVA/ritonavir: Interaction not evaluated</p>	<p>less effective due to decreased amprenavir plasma concentrations.</p>
<p>HMG-CoA reductase inhibitor: 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/nasal steroid: Fluticasone</p>	<p>LEXIVA: ↑Fluticasone</p> <p>LEXIVA/ritonavir: ↑Fluticasone</p>	<p>Use with caution. Consider alternatives to fluticasone, particularly for long-term use.</p> <p>May result in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushings 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.</p>
<p>Narcotic analgesic: Methadone</p>	<p>↓Methadone</p>	<p>Data suggest that the interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms.</p>
<p>Oral contraceptives: Ethinyl estradiol/norethin-drone^a</p>		<p>Alternative methods of non-hormonal contraception are recommended.</p>

	<p>LEXIVA: ↓Amprenavir ↓Ethinyl estradiol</p> <p>LEXIVA/ritonavir: ↓Ethinyl estradiol</p>	<p>May lead to loss of virologic response. *</p> <p>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.</p>
<p>PDE5 inhibitors: Sildenafil, tadalafil, vardenafil</p>	<p>↑Sildenafil ↑Tadalafil ↑Vardenafil</p>	<p>May result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism.</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>
<p>Proton pump inhibitors: Esomeprazole^a, lansoprazole, omeprazole, pantoprazole, rabeprazole</p>	<p>LEXIVA: ↔Amprenavir ↑Esomeprazole</p> <p>LEXIVA/ritonavir: ↔Amprenavir ↔Esomeprazole</p>	<p>Proton pump inhibitors can be administered at the same time as a dose of LEXIVA with no change in plasma amprenavir concentrations.</p>
<p>Tricyclic antidepressants: Amitriptyline, imipramine</p>	<p>↑Tricyclics</p>	<p>Therapeutic concentration monitoring is recommended for tricyclic antidepressants.</p>

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

269 **8 USE IN SPECIFIC POPULATIONS**

270 **8.1 Pregnancy**

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

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

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

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

297 **8.3 Nursing Mothers**

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

304 **8.4 Pediatric Use**

305 The safety, pharmacokinetic profile, and virologic response of LEXIVA Oral Suspension
306 and Tablets were evaluated in pediatric patients 2 to 18 years of age in 2 open-label studies [*see*
307 *Clinical Studies (14.3)*]. No data are available for pediatric patients <2 years of age.

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

311 **8.5 Geriatric Use**

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

316 **8.6 Hepatic Impairment**

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

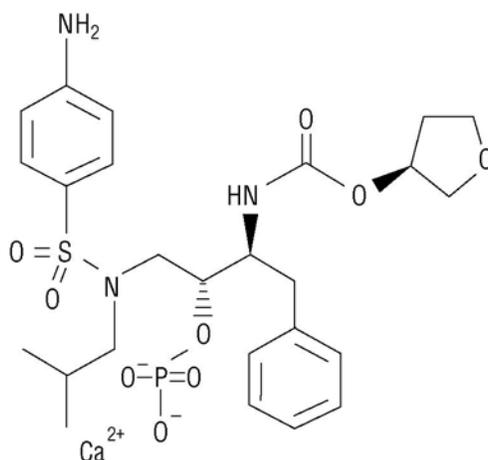
322 **10 OVERDOSAGE**

323 In a healthy volunteer repeat-dose pharmacokinetic study evaluating high-dose
324 combinations of LEXIVA plus ritonavir, an increased frequency of Grade 2/3 ALT elevations
325 (>2.5 x ULN) was observed with LEXIVA 1,400 mg twice daily plus ritonavir 200 mg twice
326 daily (4 of 25 subjects). Concurrent Grade 1/2 elevations in AST (>1.25 x ULN) were noted in 3
327 of these 4 subjects. These transaminase elevations resolved following discontinuation of dosing.

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

331 **11 DESCRIPTION**

332 LEXIVA (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of HIV
333 protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-
334 [[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonoxy) propylcarbamate
335 monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*)
336 configuration. It has a molecular formula of C₂₅H₃₄CaN₃O₉PS and a molecular weight of 623.7.
337 It has the following structural formula:
338



339
340

341 Fosamprenavir calcium is a white to cream-colored solid with a solubility of
342 approximately 0.31 mg/mL in water at 25°C.

343 LEXIVA Tablets are available for oral administration in a strength of 700 mg of
344 fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir).
345 Each 700-mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose
346 sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet
347 film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and
348 triacetin.

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

355 **12 CLINICAL PHARMACOLOGY**

356 **12.1 Mechanism of Action**

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

358 **12.3 Pharmacokinetics**

359 The pharmacokinetic properties of amprenavir after administration of LEXIVA, with or
360 without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-infected
361 patients; no substantial differences in steady-state amprenavir concentrations were observed
362 between the 2 populations.

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

365

366 **Table 7. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
 367 **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)

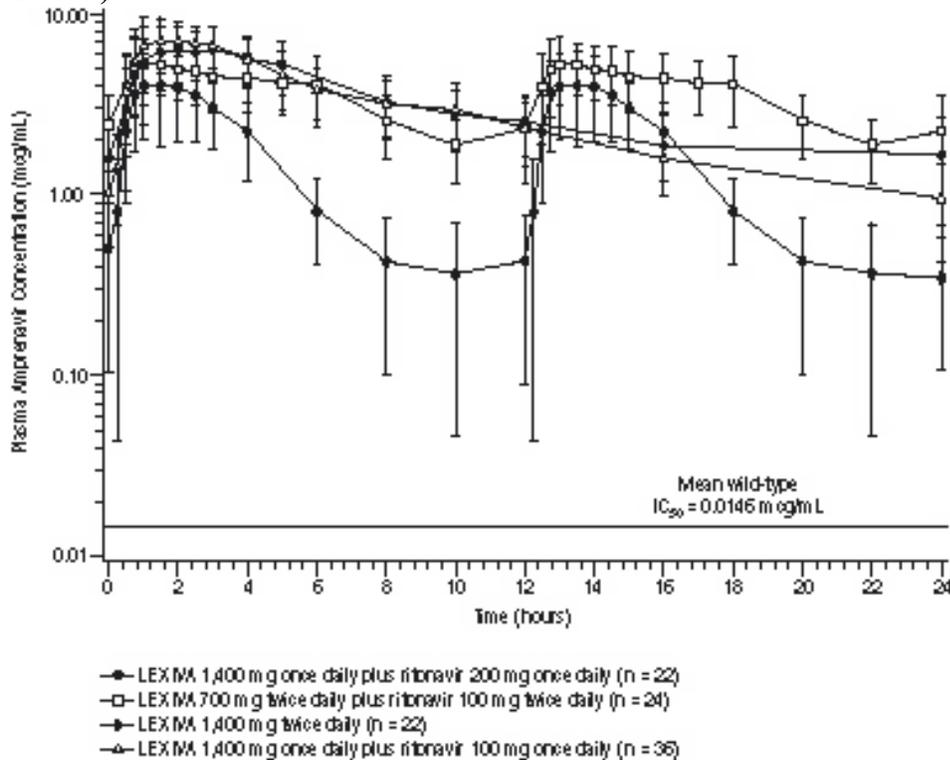
368 ^aData shown are median (range).

369

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

372

373 **Figure 1. Mean (±SD) Steady-State Plasma Amprenavir Concentrations and Mean IC₅₀**
 374 **Values Against HIV from Protease Inhibitor-Naive Patients (in the Absence of Human**
 375 **Serum)**



376

377

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

382 After administration of a single 1,400-mg dose in the fasted state, LEXIVA Oral
383 Suspension (50 mg/mL) and LEXIVA Tablets (700 mg) provided similar amprenavir exposures
384 (AUC), however, the C_{max} of amprenavir after administration of the suspension formulation was
385 14.5% higher compared with the tablet.

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

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

394 Distribution: In vitro, amprenavir is approximately 90% bound to plasma proteins,
395 primarily to α_1 -acid glycoprotein. In vitro, concentration-dependent binding was observed
396 over the concentration range of 1 to 10 mcg/mL, with decreased binding at higher
397 concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as
398 amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher
399 concentrations.

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

406 Elimination: Excretion of unchanged amprenavir in urine and feces is minimal.
407 Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged
408 amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single
409 dose of ^{14}C -amprenavir can be accounted for as metabolites in urine and feces, respectively. Two
410 metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination
411 half-life of amprenavir is approximately 7.7 hours.

412 Special Populations: Hepatic Impairment: The pharmacokinetics of amprenavir have
413 been studied after the administration of LEXIVA in combination with ritonavir to adult HIV-
414 1-infected patients with mild, moderate, and severe hepatic impairment. Following 2 weeks of
415 dosing with LEXIVA plus ritonavir, the AUC of amprenavir was increased by approximately
416 22% in patients with mild hepatic impairment, by approximately 70% in patients with moderate
417 hepatic impairment, and by approximately 80% in patients with severe hepatic impairment

418 compared with HIV-1-infected patients with normal hepatic function. Protein binding of
 419 amprenavir was decreased in patients with hepatic impairment. The unbound fraction at 2 hours
 420 (approximate C_{max}) ranged between a decrease of -7% to an increase of 57% while the unbound
 421 fraction at the end of the dosing interval (C_{min}) increased from 50% to 102% [see *Dosage and*
 422 *Administration (2.3)*].

423 The pharmacokinetics of amprenavir have been studied after administration of
 424 amprenavir given as AGENERASE® Capsules to adult patients with hepatic impairment.
 425 Following administration of a single 600-mg oral dose the AUC of amprenavir was increased by
 426 approximately 2.5-fold in patients with moderate cirrhosis and by approximately 4.5-fold in
 427 patients with severe cirrhosis compared with healthy volunteers [see *Dosage and Administration*
 428 *(2.3)*].

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

433 *Pediatric Patients:* The pharmacokinetics of amprenavir after administration of
 434 LEXIVA Oral Suspension and LEXIVA Tablets, with or without ritonavir, have been evaluated
 435 in 124 patients 2 to 18 years of age. Pharmacokinetic parameters for LEXIVA administered with
 436 food and with or without ritonavir in this patient population are provided in Tables 8 and 9
 437 below.

438
 439 **Table 8. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
 440 **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)

441

442 **Table 9. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
 443 **Parameters in Pediatric and Adolescent Patients Receiving LEXIVA Plus Ritonavir Twice**
 444 **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)

445
 446 **Geriatric Patients:** The pharmacokinetics of amprenavir after administration of
 447 LEXIVA to patients over 65 years of age have not been studied [see *Use in Specific Populations*
 448 (8.5)].

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

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

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

455 Amprenavir, the active metabolite of fosamprenavir, is metabolized in the liver by the
 456 cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Data also suggest that
 457 amprenavir induces CYP3A4. Caution should be used when coadministering medications that
 458 are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are
 459 metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19,
 460 CYP2E1, or uridine glucuronosyltransferase (UDPGT).

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

469 **Table 10. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 470 **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)
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	↔ ^g
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	↔ ^g

471 ^a Concomitant medication is also shown in this column where appropriate.
472 ^b Ritonavir C_{max}, AUC, and C_{min} increased by 63%, 45%, and 13%, respectively, compared
473 with historical control.
474 ^c Compared with historical control.
475 ^d Patients were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with
476 both ketoconazole and LEXIVA/ritonavir.
477 ^e Compared with LEXIVA 700 mg/ritonavir 100 mg b.i.d. for 2 weeks.
478 ^f Patients were receiving nevirapine for at least 12 weeks prior to study.
479 ^g Compared with parallel control group.
480 ↑= Increase; ↓= Decrease; ↔ = No change (↑ or ↓ ≤10%), NA = Not applicable.
481

482 **Table 11. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 483 **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

484 ^a Compared with parallel control group.

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

486 ^c Compared with historical data.

487 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ < 10%); NA = C_{min} not calculated for
 488 single-dose study.

489

490 **Table 12. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
 491 **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	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↓14 (↓28 to ↑4)	↔	↑28 (↑12 to ↑46)
(25-O-desacetylriofabutin metabolite)			↑579 (↑479 to ↑698)	↑1,120 (↑965 to ↑1,300)	↑2,510 (↑1,910 to ↑3,300)
Rifabutin + 25-O- desacetylriofabutin metabolite			NA	↑64 (↑46 to ↑84)	NA

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

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

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

495 0.035 mg/norethindrone 0.5 mg.

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

498 ^e Data represent lopinavir concentrations.

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

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

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

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

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

506 **Table 13. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
 507 **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
----------------------------------	-----------------------	----	---------------------	---------------------	----

508 ^a Compared with historical data.

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

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

513

514 12.4 Microbiology

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

520 Antiviral Activity: Fosamprenavir has little or no antiviral activity in vitro. The in vitro
521 antiviral activity of amprenavir was evaluated against HIV-1 IIB in both acutely and chronically
522 infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes.
523 The 50% effective concentration (EC₅₀) of amprenavir ranged from 0.012 to 0.08 μM in acutely
524 infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). The median
525 EC₅₀ value of amprenavir against HIV-1 isolates from clades A to G was 0.00095 μM in
526 peripheral blood mononuclear cells (PBMCs). Similarly, the EC₅₀ values for amprenavir against
527 monocytes/macrophage tropic HIV-1 isolates (clade B) ranged from 0.003 to 0.075 μM in
528 monocyte/macrophage cultures. The EC₅₀ values of amprenavir against HIV-2 isolates grown in
529 PBMCs were higher than those for HIV-1 isolates, and ranged from 0.003 to 0.11 μM.

530 Amprenavir exhibited synergistic anti-HIV-1 activity in combination with the nucleoside reverse
531 transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, stavudine, tenofovir, and
532 zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and
533 efavirenz; and the protease inhibitors atazanavir and saquinavir. Amprenavir exhibited additive
534 anti-HIV-1 activity in combination with the NNRTI nevirapine, the protease inhibitors indinavir,
535 lopinavir, nelfinavir, and ritonavir; and the fusion inhibitor enfuvirtide. These drug combinations
536 have not been adequately studied in humans.

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

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

557 **Cross-Resistance:** Varying degrees of cross-resistance among HIV-1 protease
 558 inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1
 559 RNA level <400 copies/mL) and protease inhibitor-resistance mutations detected in baseline
 560 HIV-1 isolates from protease inhibitor-experienced patients receiving LEXIVA/ritonavir twice
 561 daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in study APV30003 is shown in Table
 562 14. The majority of subjects had previously received either one (47%) or 2 protease inhibitors
 563 (36%), most commonly nelfinavir (57%) and indinavir (53%). Out of 102 subjects with baseline
 564 phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (n = 55) had resistance to at least one
 565 protease inhibitor, with 98% (n = 54) of those having resistance to nelfinavir. Out of 97 subjects
 566 with baseline phenotypes in the lopinavir/ritonavir arm, 60% (n = 58) had resistance to at least
 567 one protease inhibitor, with 97% (n = 56) of those having resistance to nelfinavir.

568
 569 **Table 14. Responders at Study Week 48 by Presence of Baseline Protease Inhibitor**
 570 **Resistance-Associated Mutations^a**

PI-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%

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

572 ^bMost patients had >1 protease inhibitor resistance-associated mutation at baseline.

573

574 The virologic response based upon baseline phenotype was assessed. Baseline isolates
575 from protease inhibitor-experienced patients responding to LEXIVA/ritonavir twice daily had a
576 median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of
577 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a
578 median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient
579 population, these data do not constitute definitive clinical susceptibility break points. Additional
580 data are needed to determine clinically relevant break points for LEXIVA.

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

588 **13 NONCLINICAL TOXICOLOGY**

589 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

590 In long-term carcinogenicity studies, fosamprenavir was administered orally for up to
591 104 weeks at doses of 250, 400, or 600 mg/kg/day in mice and at doses of 300, 825, or
592 2,250 mg/kg/day in rats. Exposures at these doses were 0.3- to 0.7-fold (mice) and 0.7- to
593 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to
594 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of
595 fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were
596 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir
597 plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and
598 hepatocellular carcinomas at all doses in male mice and at 600 mg/kg/day in female mice, and in
599 hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and at
600 835 mg/kg/day and 2,250 mg/kg/day in female rats. The relevance of the hepatocellular findings
601 in the rodents for humans is uncertain. Repeat dose studies with fosamprenavir in rats produced
602 effects consistent with enzyme induction, which predisposes rats, but not humans, to thyroid
603 neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at
604 825 mg/kg/day and 2,250 mg/kg/day, and an increase in uterine endometrial adenocarcinoma at
605 2,250 mg/kg/day. The incidence of endometrial findings was slightly increased over concurrent
606 controls, but was within background range for female rats. The relevance of the uterine
607 endometrial adenocarcinoma findings in rats for humans is uncertain.

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

611 The effects of fosamprenavir on fertility and general reproductive performance were
612 investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks

613 before mating through postpartum day 6). Systemic exposures (AUC_{0-24 hr}) to amprenavir in
 614 these studies were 3 (males) to 4 (females) times higher than exposures in humans following
 615 administration of the MRHD of fosamprenavir alone or similar to those seen in humans
 616 following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not
 617 impair mating or fertility of male or female rats and did not affect the development and
 618 maturation of sperm from treated rats.

619 **14 CLINICAL STUDIES**

620 **14.1 Therapy-Naive Adult Patients**

621 Study APV30001: APV30001 was a randomized, open-label study, comparing
 622 treatment with LEXIVA Tablets (1,400 mg twice daily) versus nelfinavir (1,250 mg twice daily)
 623 in 249 antiretroviral treatment-naive patients. Both groups of patients also received abacavir
 624 (300 mg twice daily) and lamivudine (150 mg twice daily).

625 The mean age of the patients in this study was 37 years (range: 17 to 70 years), 69% of
 626 the patients were males, 20% were CDC Class C (AIDS), 24% were Caucasian, 32% were black,
 627 and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells/mm³ (range: 2 to
 628 1,136 cells/mm³; 18% of patients had a CD4+ cell count of <50 cells/mm³ and 30% were in the
 629 range of 50 to <200 cells/mm³). Baseline median HIV-1 RNA was 4.83 log₁₀ copies/mL (range:
 630 1.69 to 7.41 log₁₀ copies/mL; 45% of patients had >100,000 copies/mL).

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

632
 633 **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%

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

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

638
 639 Treatment response by viral load strata is shown in Table 16.

640

641 **Table 16. Proportions of Responders Through Week 48 by Screening Viral Load**
 642 **(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

643
 644 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
 645 were 201 cells/mm³ in the group receiving LEXIVA and 216 cells/mm³ in the nelfinavir group.

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

650 The mean age of the patients in this study was 37 years (range: 18 to 69 years), 73% of
 651 the patients were males, 22% were CDC Class C, 53% were Caucasian, 36% were black, and 8%
 652 were Hispanic. At baseline, the median CD4+ cell count was 170 cells/mm³ (range: 1 to
 653 1,055 cells/mm³; 20% of patients had a CD4+ cell count of <50 cells/mm³ and 35% were in the
 654 range of 50 to <200 cells/mm³). Baseline median HIV-1 RNA was 4.81 log₁₀ copies/mL (range:
 655 2.65 to 7.29 log₁₀ copies/mL; 43% of patients had >100,000 copies/mL).

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

657
 658 **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%

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

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

663
 664 Treatment response by viral load strata is shown in Table 18.

665

666 **Table 18. Proportions of Responders Through Week 48 by Screening Viral Load**
 667 **(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

668
 669 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
 670 were 203 cells/mm³ in the group receiving LEXIVA and 207 cells/mm³ in the nelfinavir group.

671 **14.2 Protease Inhibitor-Experienced Adult Patients**

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

677 The mean age of the patients in this study was 42 years (range: 24 to 72 years), 85% were
 678 male, 33% were CDC Class C, 67% were Caucasian, 24% were black, and 9% were Hispanic.
 679 The median CD4+ cell count at baseline was 263 cells/mm³ (range: 2 to 1,171 cells/mm³).
 680 Baseline median plasma HIV-1 RNA level was 4.14 log₁₀ copies/mL (range: 1.69 to
 681 6.41 log₁₀ copies/mL).

682 The median durations of prior exposure to NRTIs were 257 weeks for patients receiving
 683 LEXIVA/ritonavir twice daily (79% had ≥3 prior NRTIs) and 210 weeks for patients receiving
 684 lopinavir/ritonavir (64% had ≥3 prior NRTIs). The median durations of prior exposure to
 685 protease inhibitors were 149 weeks for patients receiving LEXIVA/ritonavir twice daily (49%
 686 received ≥2 prior protease inhibitors) and 130 weeks for patients receiving lopinavir/ritonavir
 687 (40% received ≥2 prior protease inhibitors).

688 The time-averaged changes in plasma HIV-1 RNA from baseline (AAUCMB) at
 689 48 weeks (the endpoint on which the study was powered) were -1.4 log₁₀ copies/mL for
 690 twice-daily LEXIVA/ritonavir and -1.67 log₁₀ copies/mL for the lopinavir/ritonavir group.

691 The proportions of patients who achieved and maintained confirmed HIV-1 RNA
 692 <400 copies/mL (secondary efficacy endpoint) were 58% with twice-daily LEXIVA/ritonavir
 693 and 61% with lopinavir/ritonavir (95% CI for the difference: -16.6, 10.1). The proportions of
 694 patients with HIV-1 RNA <50 copies/mL with twice-daily LEXIVA/ritonavir and with
 695 lopinavir/ritonavir were 46% and 50%, respectively (95% CI for the difference: -18.3, 8.9). The
 696 proportions of patients who were virologic failures were 29% with twice-daily
 697 LEXIVA/ritonavir and 27% with lopinavir/ritonavir.

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

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

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

704 Once-daily administration of LEXIVA plus ritonavir is not recommended for protease
705 inhibitor-experienced patients. Through Week 48, 50% and 37% of patients receiving LEXIVA
706 1,400 mg plus ritonavir 200 mg once daily had plasma HIV-1 RNA <400 copies/mL and
707 <50 copies/mL, respectively.

708 **14.3 Pediatric Patients**

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

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

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

724 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

727 Bottle of 60 with child-resistant closure (NDC 0173-0721-00).

728 Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C
729 (59° to 86°F) (see USP Controlled Room Temperature). Keep container tightly closed.

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

733 Bottle of 225 mL with child-resistant closure (NDC 0173-0727-00).

734 This product does not require reconstitution.

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

736 **17 PATIENT COUNSELING INFORMATION**

737 *See FDA-approved Patient Labeling.*

738 **17.1 Drug Interactions**

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

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

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

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

750 **17.2 Sulfa Allergy**

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

753 **17.3 Redistribution/Accumulation of Body Fat**

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

757 **17.4 Information About Therapy With LEXIVA**

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

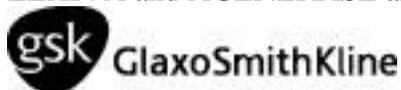
763 Patients should be told that sustained decreases in plasma HIV-1 RNA have been
764 associated with a reduced risk of progression to AIDS and death. Patients should remain under
765 the care of a physician while using LEXIVA. Patients should be advised to take LEXIVA every
766 day as prescribed. LEXIVA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

770 **17.5 Oral Suspension**

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

773

774 LEXIVA and AGENERASE are registered trademarks of GlaxoSmithKline.



775 GlaxoSmithKline
776 Research Triangle Park, NC 27709

Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

777
778 ©2009, GlaxoSmithKline. All rights reserved.

779
780
781 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

782 -----
783

784 **PATIENT INFORMATION**

785
786 **LEXIVA[®]**
787 (lex-EE-vah)
788 **(fosamprenavir calcium)**
789 **Tablets and Oral Suspension**
790

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

797
798 **What is the most important information I should know about LEXIVA?**

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

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

805
806 Know all the medicines you take, including prescription and nonprescription medicines,
807 vitamins, and herbal supplements. Keep a list of the medicines you take. Show this list to all your
808 healthcare providers and pharmacists anytime you get a new medicine or refill. Your healthcare
809 providers and pharmacists must know all the medicines you take. They will tell you if you can
810 take other medicines with LEXIVA. Do not start any new medicines while you are taking
811 LEXIVA without talking with your healthcare provider or pharmacist. You can ask your
812 healthcare provider or pharmacist for a list of medicines that can interact with LEXIVA.

813
814 **What is LEXIVA?**

815 LEXIVA is a medicine you take by mouth to treat HIV infection. HIV is the virus that causes
816 AIDS (acquired immune deficiency syndrome). LEXIVA belongs to a class of anti-HIV
817 medicines called protease inhibitors. LEXIVA is always used with other anti-HIV medicines.
818 When used in combination therapy, LEXIVA may help lower the amount of HIV found in your
819 blood, raise CD4+ (T) cell counts, and keep your immune system as healthy as possible, so it can
820 help fight infection. However, LEXIVA does not work in all patients with HIV.

821

822 **LEXIVA does not:**

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

833

834 LEXIVA has not been fully studied in children under the age of 2 or in adults over the age of 65.

835

836 **Who should not take LEXIVA?**

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

- 838 • are taking certain other medicines. Read the section “What is the most important information I
839 should know about LEXIVA?” Do not take the following medicines* with LEXIVA. You
840 could develop serious or life-threatening problems.
 - 841 • HALCION[®] (triazolam; used for insomnia)
 - 842 • Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine
843 such as CAFERGOT[®], MIGRANAL[®], D.H.E. 45[®], ergotrate maleate, METHERGINE[®],
844 and others (used for migraine headaches)
 - 845 • PROPULSID[®] (cisapride), used for certain stomach problems
 - 846 • VERSED[®] (midazolam), used for sedation
 - 847 • ORAP[®] (pimozide), used for Tourette’s disorder
- 848 • are allergic to LEXIVA or any of its ingredients. The active ingredient is fosamprenavir
849 calcium. See the end of this leaflet for a list of all the ingredients in LEXIVA.
- 850 • are allergic to AGENERASE (amprenavir).

851

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

853

854 There are other medicines you should not take if you are taking LEXIVA and NORVIR®
855 (ritonavir) together. You could develop serious or life-threatening problems. Tell your healthcare
856 provider about all medicines you are taking before you begin taking LEXIVA and NORVIR
857 (ritonavir) together.

858

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

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

- 862 • are pregnant or planning to become pregnant. It is not known if LEXIVA can harm your
863 unborn baby. You and your healthcare provider will need to decide if LEXIVA is right for
864 you. If you use LEXIVA while you are pregnant, talk to your healthcare provider about how
865 you can be on the Antiretroviral Pregnancy Registry.
- 866 • are breastfeeding. You should not breastfeed if you are HIV-positive because of the chance of
867 passing the HIV virus to your baby through your milk. Also, it is not known if LEXIVA can
868 pass into your breast milk and if it can harm your baby. If you are a woman who has or will
869 have a baby, talk with your healthcare provider about the best way to feed your baby.
- 870 • have liver problems. You may be given a lower dose of LEXIVA or LEXIVA may not be
871 right for you.
- 872 • have kidney problems
- 873 • have diabetes. You may need dose changes in your insulin or other diabetes medicines.
- 874 • have hemophilia
- 875 • are allergic to sulfa medicines

876

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

884

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

889

890 **How should I take LEXIVA?**

- 891 • Take LEXIVA exactly as your healthcare provider prescribed.
- 892 • Do not take more or less than your prescribed dose of LEXIVA at any one time. Do not
893 change your dose or stop taking LEXIVA without talking with your healthcare provider.

- 894 • You can take LEXIVA Tablets with or without food.
- 895 • Adults should take LEXIVA Oral Suspension without food.
- 896 • Pediatric patients should take LEXIVA Oral Suspension with food. If vomiting occurs within
897 30 minutes after dosing, the dose should be repeated.
- 898 • Shake LEXIVA Oral Suspension vigorously before each use.
- 899 • When your supply of LEXIVA or other anti-HIV medicine starts to run low, get more from
900 your healthcare provider or pharmacy. The amount of HIV virus in your blood may increase if
901 one or more of the medicines are stopped, even for a short time.
- 902 • Stay under the care of a healthcare provider while using LEXIVA.
- 903 • It is important that you do not miss any doses. If you miss a dose of LEXIVA by more than
904 4 hours, wait and take the next dose at the regular time. However, if you miss a dose by fewer
905 than 4 hours, take your missed dose right away. Then take your next dose at the regular time.
- 906 • If you take too much LEXIVA, call your healthcare provider or poison control center right
907 away.

908

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

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

922

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

924 LEXIVA may cause the following side effects:

- 925 • skin rash. Skin rashes, some with itching, have happened in patients taking LEXIVA.
926 Swelling of the face, lips, and tongue (angioedema) has also been reported. Tell your
927 healthcare provider if you get a rash or develop facial swelling after starting LEXIVA.
- 928 • diabetes and high blood sugar (hyperglycemia). Some patients had diabetes before taking
929 LEXIVA while others did not. Some patients may need changes in their diabetes medicine.
930 Others may need a new diabetes medicine.
- 931 • increased bleeding problems in some patients with hemophilia.
- 932 • worse liver disease. Patients with liver problems, including hepatitis B or C, are more likely to
933 get worse liver disease when they take anti-HIV medicines like LEXIVA.

- 934 • changes in blood tests. Some people have changes in blood tests while taking LEXIVA. These
935 include increases seen in liver function tests and blood fat levels, and decreases in white blood
936 cells. Your healthcare provider may do regular blood tests to see if LEXIVA is affecting your
937 body.
- 938 • changes in body fat. These changes have happened in patients taking antiretroviral medicines
939 like LEXIVA. The changes may include an increased amount of fat in the upper back and
940 neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face
941 may also happen. The cause and long-term health effects of these conditions are not known at
942 this time.
- 943 • kidney stones have been reported in some patients taking LEXIVA. If you develop signs or
944 symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) tell
945 your healthcare provider right away.

946

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

949

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

952

953 **How should I store LEXIVA?**

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

961

962 **General information about LEXIVA**

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

966

967 This leaflet summarizes the most important information about LEXIVA. If you would like more
968 information, talk with your healthcare provider. You can ask your pharmacist or healthcare
969 provider for information about LEXIVA that is written for health professionals. For more
970 information you can call toll-free 888-825-5249 or visit www.LEXIVA.com.

971

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

973 Tablets:

974 Active Ingredient: fosamprenavir calcium.

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

978
979 LEXIVA Tablets, 700 mg, are pink in color and are capsule-shaped, with the letters “GX LL7”
980 printed on one side of the tablet.



981

982

983 Oral Suspension:

984 Active Ingredient: fosamprenavir calcium

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

988

989 LEXIVA and AGENERASE are registered trademarks of GlaxoSmithKline.

990

991 * The brands listed are trademarks of their respective owners and are not trademarks of
992 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
993 GlaxoSmithKline or its products.

994

995



996 GlaxoSmithKline
997 Research Triangle Park, NC 27709

Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

998

999 ©2009, GlaxoSmithKline. All rights reserved.

1000

1001 September 2009

1002 LXV:7PIL