

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, for oral use
LEXIVA (fosamprenavir calcium) Oral Suspension
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage (1) 04/2012
Dosage and Administration, Pediatric Patients (2.2, 2.3) 04/2012

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 (aged at least 4 weeks to 18 years): 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 per mL oral suspension (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Certain drugs should not be coadministered with LEXIVA due to risk of serious or life-threatening adverse reactions. (5.1)
- LEXIVA should be discontinued for severe skin reactions including Stevens-Johnson syndrome. (5.2)
- LEXIVA should be used with caution in patients with a known sulfonamide allergy. (5.3)
- Use of higher than approved doses may lead to transaminase elevations. Patients with hepatitis B or C are at increased risk of transaminase elevations. (5.4)
- Patients receiving LEXIVA may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.5), immune reconstitution syndrome (5.6), redistribution/accumulation of body fat (5.7), and elevated triglyceride and cholesterol concentrations (5.8). Monitor cholesterol and triglycerides prior to therapy and periodically thereafter.
- Acute hemolytic anemia has been reported with amprenavir. (5.9)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.10)
- Nephrolithiasis: Cases of nephrolithiasis have been reported with fosamprenavir. (5.11)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

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

Revised: 02/2013

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*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 [see *Dosage and Administration (2.1,*
12 *2.2)*, *Clinical Studies (14.2, 14.3)*].
- 13 • Dosing of LEXIVA plus ritonavir is not recommended for protease inhibitor-experienced
14 pediatric patients younger than 6 months [see *Clinical Pharmacology (12.3)*].

15 2 DOSAGE AND ADMINISTRATION

16 LEXIVA Tablets may be taken with or without food.

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

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

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

24 2.1 Adults

25 Therapy-Naive Adults:

- 26 • LEXIVA 1,400 mg twice daily (without ritonavir).
- 27 • LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily.
- 28 • LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily.
 - 29 ○ Dosing of LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily is
 - 30 supported by pharmacokinetic data [see *Clinical Pharmacology (12.3)*].
- 31 • LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily.
 - 32 ○ Dosing of LEXIVA 700 mg twice daily plus 100 mg ritonavir twice daily is
 - 33 supported by pharmacokinetic and safety data [see *Clinical Pharmacology (12.3)*].

34 Protease Inhibitor-Experienced Adults:

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

36 2.2 Pediatric Patients (Aged at Least 4 Weeks to 18 Years)

37 The recommended dosage of LEXIVA in patients aged at least 4 weeks to 18 years
38 should be calculated based on body weight (kg) and should not exceed the recommended adult
39 dose (Table 1).
40

41 **Table 1. Twice-Daily Dosage Regimens by Weight for Protease Inhibitor-Naive**
42 **Pediatric Patients (Greater Than or Equal to 4 Weeks of Age) and for Protease**
43 **Inhibitor-Experienced Pediatric Patients (Greater Than or Equal to 6 Months of**
44 **Age) Using LEXIVA Oral Suspension With Concurrent Ritonavir**

Weight	Twice-Daily Dosage Regimen
<11 kg	LEXIVA 45 mg/kg plus ritonavir 7 mg/kg ^a
11 kg - <15 kg	LEXIVA 30 mg/kg plus ritonavir 3 mg/kg ^a
15 kg - <20 kg	LEXIVA 23 mg/kg plus ritonavir 3 mg/kg ^a
≥20 kg	LEXIVA 18 mg/kg plus ritonavir 3 mg/kg ^a

45 ^a When dosing with ritonavir, do not exceed the adult dose of LEXIVA 700 mg/
46 ritonavir 100 mg twice-daily dose.
47

48 Alternatively, protease inhibitor-naive children aged 2 years and older can be
49 administered LEXIVA (without ritonavir) 30 mg per kg twice daily.

50 LEXIVA should only be administered to infants born at 38 weeks gestation or greater and
51 who have attained a post-natal age of 28 days.

52 For pediatric patients, pharmacokinetic and clinical data:

- 53 • do not support once-daily dosing of LEXIVA alone or in combination with ritonavir [*see*
54 *Clinical Studies (14.3)*].
- 55 • do not support administration of LEXIVA alone or in combination with ritonavir for protease
56 inhibitor-experienced children younger than 6 months [*see Clinical Pharmacology (12.3)*].
- 57 • do not support twice-daily dosing of LEXIVA without ritonavir in pediatric patients younger
58 than 2 years [*see Clinical Pharmacology (12.3)*].

59 **Other Dosing Considerations:**

- 60 • When administered without ritonavir, the adult regimen of LEXIVA Tablets 1,400 mg twice
61 daily may be used for pediatric patients weighing at least 47 kg.
- 62 • When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric
63 patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients
64 weighing at least 33 kg.

65 **2.3 Patients With Hepatic Impairment**

66 *See Clinical Pharmacology (12.3).*

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

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

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

79 There are no data to support dosing recommendations for pediatric patients with hepatic
80 impairment.

81 **3 DOSAGE FORMS AND STRENGTHS**

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

84 LEXIVA Oral Suspension, 50 mg per mL, is a white to off-white suspension that has a
85 characteristic grape-bubblegum-peppermint flavor.

86 **4 CONTRAINDICATIONS**

87 LEXIVA is contraindicated:

- 88 • in patients with previously demonstrated clinically significant hypersensitivity (e.g.,
89 Stevens-Johnson syndrome) to any of the components of this product or to amprenavir.
- 90 • when coadministered with drugs that are highly dependent on cytochrome P450 3A4
91 (CYP3A4) for clearance and for which elevated plasma concentrations are associated with
92 serious and/or life-threatening events (Table 2).

93

94 **Table 2. Drugs Contraindicated With LEXIVA (Information in the table applies to**
 95 **LEXIVA with or without ritonavir, unless otherwise indicated.)**

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

96 ^a See *Clinical Pharmacology (12.3) Tables 10, 11, 12, or 13 for magnitude of interaction.*
 97

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

101 **5 WARNINGS AND PRECAUTIONS**

102 **5.1 Drug Interactions**

103 See Table 2 for listings of drugs that are contraindicated due to potentially
104 life-threatening adverse events, significant drug interactions, or loss of virologic activity [*see*
105 *Contraindications (4), Drug Interactions (7.2)*]. See Table 7 for a listing of established and other
106 potentially significant drug interactions [*see Drug Interactions (7.3)*].

107 **5.2 Skin Reactions**

108 Severe and life-threatening skin reactions, including 1 case of Stevens-Johnson syndrome
109 among 700 subjects treated with LEXIVA in clinical trials. Treatment with LEXIVA should be
110 discontinued for severe or life-threatening rashes and for moderate rashes accompanied by
111 systemic symptoms [*see Adverse Reactions (6)*].

112 **5.3 Sulfa Allergy**

113 LEXIVA should be used with caution in patients with a known sulfonamide allergy.
114 Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs
115 in the sulfonamide class and fosamprenavir is unknown. In a clinical trial of LEXIVA used as
116 the sole protease inhibitor, rash occurred in 2 of 10 subjects (20%) with a history of sulfonamide
117 allergy compared with 42 of 126 subjects (33%) with no history of sulfonamide allergy. In
118 2 clinical trials of LEXIVA plus low-dose ritonavir, rash occurred in 8 of 50 subjects (16%) with
119 a history of sulfonamide allergy compared with 50 of 412 subjects (12%) with no history of
120 sulfonamide allergy.

121 **5.4 Hepatic Toxicity**

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

128 **5.5 Diabetes/Hyperglycemia**

129 New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and
130 hyperglycemia have been reported during postmarketing surveillance in HIV-1-infected patients
131 receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments
132 of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic
133 ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy,
134 hyperglycemia persisted in some cases. Because these events have been reported voluntarily
135 during clinical practice, estimates of frequency cannot be made and causal relationships between
136 protease inhibitor therapy and these events have not been established.

137 **5.6 Immune Reconstitution Syndrome**

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

144 Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré
145 syndrome) have also been reported to occur in the setting of immune reconstitution; however, the
146 time to onset is more variable, and can occur many months after initiation of treatment.

147 **5.7 Fat Redistribution**

148 Redistribution/accumulation of body fat, including central obesity, dorsocervical fat
149 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and
150 "cushingoid appearance," have been observed in patients receiving antiretroviral therapy,
151 including LEXIVA. The mechanism and long-term consequences of these events are currently
152 unknown. A causal relationship has not been established.

153 **5.8 Lipid Elevations**

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

158 **5.9 Hemolytic Anemia**

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

160 **5.10 Patients With Hemophilia**

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

165 **5.11 Nephrolithiasis**

166 Cases of nephrolithiasis were reported during postmarketing surveillance in HIV-1-
167 infected patients receiving LEXIVA. Because these events were reported voluntarily during
168 clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis
169 occur, temporary interruption or discontinuation of therapy may be considered.

170 **5.12 Resistance/Cross-Resistance**

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

175 **6 ADVERSE REACTIONS**

- 176 • Severe or life-threatening skin reactions have been reported with the use of LEXIVA [*see*
177 *Warnings and Precautions (5.2)*].
- 178 • The most common moderate to severe adverse reactions in clinical trials of LEXIVA were
179 diarrhea, rash, nausea, vomiting, and headache.
- 180 • Treatment discontinuation due to adverse events occurred in 6.4% of subjects receiving
181 LEXIVA and in 5.9% of subjects receiving comparator treatments. The most common
182 adverse reactions leading to discontinuation of LEXIVA (incidence less than or equal to 1%
183 of subjects) included diarrhea, nausea, vomiting, AST increased, ALT increased, and rash.

184 **6.1 Clinical Trials**

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

188 Adult Trials: The data for the 3 active-controlled clinical trials described below reflect
189 exposure of 700 HIV-1–infected subjects to LEXIVA Tablets, including 599 subjects exposed to
190 LEXIVA for greater than 24 weeks, and 409 subjects exposed for greater than 48 weeks. The
191 population age ranged from 17 to 72 years. Of these subjects, 26% were female, 51% Caucasian,
192 31% black, 16% American Hispanic, and 70% were antiretroviral-naïve. Sixty-one percent
193 received LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily; 24% received
194 LEXIVA 1,400 mg twice daily; and 15% received LEXIVA 700 mg twice daily plus ritonavir
195 100 mg twice daily.

196 Selected adverse reactions reported during the clinical efficacy trials of LEXIVA are
197 shown in Tables 3 and 4. Each table presents adverse reactions of moderate or severe intensity in
198 subjects treated with combination therapy for up to 48 weeks.

199

200 **Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater Than**
 201 **or Equal to 2% of Antiretroviral-Naive Adult Subjects**

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%

202 ^a All subjects also received abacavir and lamivudine twice daily.

203
 204 **Table 4. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater Than**
 205 **or Equal to 2% of Protease Inhibitor-Experienced Adult Subjects (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%

206 ^a All subjects also received 2 reverse transcriptase inhibitors.

207
 208 Skin rash (without regard to causality) occurred in approximately 19% of subjects treated
 209 with LEXIVA in the pivotal efficacy trials. Rashes were usually maculopapular and of mild or
 210 moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of

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

215 The percentages of subjects with Grade 3 or 4 laboratory abnormalities in the clinical
 216 efficacy trials of LEXIVA are presented in Tables 5 and 6.

217

218 **Table 5. Grade 3/4 Laboratory Abnormalities Reported in Greater Than or Equal to 2%**
 219 **of Antiretroviral-Naive Adult Subjects 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%

220 ^a All subjects also received abacavir and lamivudine twice daily.

221 ^b Fasting specimens.

222 ULN = Upper limit of normal.

223

224 The incidence of Grade 3 or 4 hyperglycemia in antiretroviral-naive subjects who
 225 received LEXIVA in the pivotal trials was less than 1%.

226

227 **Table 6. Grade 3/4 Laboratory Abnormalities Reported in Greater Than or Equal to 2%**
 228 **of Protease Inhibitor-Experienced Adult Subjects 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

229 ^a All subjects also received 2 reverse transcriptase inhibitors.

230 ^b Fasting specimens.

231 ^c n = 100 for LEXIVA plus ritonavir, n = 98 for lopinavir plus ritonavir.

232 ULN = Upper limit of normal.

233

234 **Pediatric Trials:** LEXIVA with and without ritonavir was studied in 237 HIV-1–infected
 235 pediatric subjects aged at least 4 weeks to 18 years in 3 open-label trials, APV20002,
 236 APV20003, and APV29005 [see *Clinical Studies (14.3)*]. Vomiting and neutropenia occurred
 237 more frequently in pediatric subjects compared to adults. Other adverse events occurred with
 238 similar frequency in pediatric subjects compared with adults.

239 The frequency of vomiting among pediatric subjects receiving LEXIVA twice daily with
 240 ritonavir was 20% in subjects aged at least 4 weeks to less than 2 years and 36% in subjects aged
 241 2 to 18 years compared with 10% in adults. The frequency of vomiting among pediatric subjects
 242 receiving LEXIVA twice daily without ritonavir was 60% in subjects aged 2 to 5 years compared
 243 with 16% in adults.

244 The median duration of drug-related vomiting episodes in APV29005 was 1 day (range: 1
 245 to 3 days), in APV20003 was 16 days (range: 1 to 38 days), and in APV20002 was 9 days
 246 (range: 4 to 13 days). Vomiting was treatment limiting in 4 pediatric subjects across all 3 trials.

247 The incidence of Grade 3 or 4 neutropenia (neutrophils less than 750 cells per mm³) seen
 248 in pediatric subjects treated with LEXIVA with and without ritonavir was higher (15%) than the
 249 incidence seen in adult subjects (3%). Grade 3/4 neutropenia occurred in 10% (5/51) of subjects
 250 aged at least 4 weeks to less than 2 years and 16% (28/170) of subjects aged 2 to 18 years.

251 **6.2 Postmarketing Experience**

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

257 **Cardiac Disorders:** Myocardial infarction.

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

259 Nervous System Disorders: Oral paresthesia.
 260 Skin and Subcutaneous Tissue Disorders: Angioedema.
 261 Urogenital: Nephrolithiasis.

262 **7 DRUG INTERACTIONS**

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

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

266 **7.1 Cytochrome P450 Inhibitors and Inducers**

267 Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of CYP3A4
 268 metabolism and therefore should not be administered concurrently with medications with narrow
 269 therapeutic windows that are substrates of CYP3A4. Data also suggest that amprenavir induces
 270 CYP3A4.

271 Amprenavir is metabolized by CYP3A4. Coadministration of LEXIVA and drugs that
 272 induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its
 273 therapeutic effect. Coadministration of LEXIVA and drugs that inhibit CYP3A4 may increase
 274 amprenavir concentrations and increase the incidence of adverse effects.

275 The potential for drug interactions with LEXIVA changes when LEXIVA is
 276 coadministered with the potent CYP3A4 inhibitor ritonavir. The magnitude of
 277 CYP3A4-mediated drug interactions (effect on amprenavir or effect on coadministered drug)
 278 may change when LEXIVA is coadministered with ritonavir. Because ritonavir is a CYP2D6
 279 inhibitor, clinically significant interactions with drugs metabolized by CYP2D6 are possible
 280 when coadministered with LEXIVA plus ritonavir.

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

283 **7.2 Drugs That Should Not Be Coadministered With LEXIVA**

284 *See Contraindications (4).*

285 **7.3 Established and Other Potentially Significant Drug Interactions**

286 Table 7 provides a listing of established or potentially clinically significant drug
 287 interactions. Information in the table applies to LEXIVA with or without ritonavir, unless
 288 otherwise indicated.

289

290 **Table 7. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
<i>HCV/HIV-Antiviral Agents</i>		

<p>HCV protease inhibitor: Telaprevir^a</p>	<p>LEXIVA/ritonavir: ↓Amprenavir ↓Telaprevir</p>	<p>Coadministration of LEXIVA/ritonavir and telaprevir is not recommended.</p>
<p>HCV protease inhibitor: Boceprevir</p>	<p>LEXIVA/ritonavir: ↓Amprenavir (predicted) ↓Boceprevir (predicted)</p>	<p>Coadministration of LEXIVA/ritonavir and boceprevir is not recommended.</p> <p>A pharmacokinetic interaction has been reported between boceprevir and some HIV protease inhibitors in combination with ritonavir, leading to decreased HIV protease inhibitor concentrations and, in some cases, decreased boceprevir concentrations.</p>
<p>Non-nucleoside reverse transcriptase inhibitor: Efavirenz^a</p>	<p>LEXIVA: ↓Amprenavir</p> <p>LEXIVA/ritonavir: ↓Amprenavir</p>	<p>Appropriate doses of the combinations with respect to safety and efficacy have not been established.</p> <p>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.</p>
<p>Non-nucleoside reverse transcriptase inhibitor: Nevirapine^a</p>	<p>LEXIVA: ↓Amprenavir ↑Nevirapine</p> <p>LEXIVA/ritonavir: ↓Amprenavir ↑Nevirapine</p>	<p>Coadministration of nevirapine and LEXIVA without ritonavir is not recommended.</p> <p>No dosage adjustment required when nevirapine is administered with LEXIVA/ritonavir twice daily.</p> <p>The combination of nevirapine administered with LEXIVA/ritonavir once-daily regimen has not been studied.</p>
<p>HIV protease inhibitor: Atazanavir^a</p>	<p>LEXIVA: Interaction has not</p>	<p>Appropriate doses of the combinations with respect to safety and efficacy have</p>

	<p>been evaluated.</p> <p>LEXIVA/ritonavir: ↓Atazanavir ↔Amprenavir</p>	not been established.
<p>HIV protease inhibitors: Indinavir^a, nelfinavir^a</p>	<p>LEXIVA: ↑Amprenavir</p> <p>Effect on indinavir and nelfinavir is not well established.</p> <p>LEXIVA/ritonavir: Interaction has not been evaluated.</p>	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
<p>HIV protease inhibitors: Lopinavir/ritonavir^a</p>	<p>↓Amprenavir ↓Lopinavir</p>	An increased rate of adverse events has been observed. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
<p>HIV protease inhibitor: Saquinavir^a</p>	<p>LEXIVA: ↓Amprenavir</p> <p>Effect on saquinavir is not well established.</p> <p>LEXIVA/ritonavir: Interaction has not been evaluated.</p>	Appropriate doses of the combination with respect to safety and efficacy have not been established.
<p>HIV integrase inhibitor: Raltegravir^a</p>	<p>LEXIVA: ↓Amprenavir ↓Raltegravir</p> <p>LEXIVA/ritonavir: ↓Amprenavir ↓Raltegravir</p>	Appropriate doses of the combination with respect to safety and efficacy have not been established.

HIV CCR5 co-receptor antagonist: Maraviroc ^a	LEXIVA/ritonavir: ↓Amprenavir ↑Maraviroc	No dosage adjustment required for LEXIVA/ritonavir. The recommended dose of maraviroc is 150 mg twice daily when coadministered with LEXIVA/ritonavir. LEXIVA should be given with ritonavir when coadministered with maraviroc.
<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.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin Phenytoin ^a	LEXIVA: ↓Amprenavir LEXIVA/ritonavir: ↑Amprenavir ↓Phenytoin	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Plasma phenytoin concentrations should be monitored and phenytoin dose should be increased as appropriate. No change in LEXIVA/ritonavir dose is recommended.
Antidepressant: Paroxetine, trazodone	↓Paroxetine ↑Trazodone	Coadministration of paroxetine with LEXIVA/ritonavir significantly decreased plasma levels of paroxetine. Any paroxetine dose adjustment should be guided by clinical effect (tolerability and efficacy). Concomitant use of trazodone and LEXIVA with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration

		of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as LEXIVA, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals: Ketoconazole ^a , itraconazole	↑Ketoconazole ↑Itraconazole	Increase monitoring for adverse events. LEXIVA: Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day. LEXIVA/ritonavir: High doses of ketoconazole or itraconazole (greater than 200 mg/day) are not recommended.
Anti-gout: Colchicine	↑Colchicine	Patients with renal or hepatic impairment should not be given colchicine with LEXIVA/ritonavir. LEXIVA/ritonavir and coadministration of colchicine: Treatment of gout flares: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF):

		<p>Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p> <p>LEXIVA and coadministration of colchicine:</p> <p>Treatment of gout flares: 1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg twice a day or 0.6 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once a day.</p> <p>Treatment of FMF: Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day).</p>
<p>Antimycobacterial: Rifabutin^a</p>	<p>↑Rifabutin and rifabutin metabolite</p>	<p>A complete blood count should be performed weekly and as clinically indicated to monitor for neutropenia.</p> <p>LEXIVA: A dosage reduction of rifabutin by at least half the recommended dose is required.</p> <p>LEXIVA/ritonavir: Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).</p>
<p>Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam</p>	<p>↑Benzodiazepines</p>	<p>Clinical significance is unknown. A decrease in benzodiazepine dose may be needed.</p>
<p>Calcium channel</p>	<p>↑Calcium channel</p>	<p>Use with caution. Clinical monitoring of</p>

blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	blockers	patients is recommended.
Corticosteroid: Dexamethasone	↓Amprenavir	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations.
Endothelin-receptor antagonists: Bosentan	↑Bosentan	Coadministration of bosentan in patients on LEXIVA: In patients who have been receiving LEXIVA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Coadministration of LEXIVA in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of LEXIVA. After at least 10 days following the initiation of LEXIVA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Histamine H₂-receptor antagonists: Cimetidine, famotidine, nizatidine, ranitidine ^a	LEXIVA: ↓Amprenavir LEXIVA/ritonavir: Interaction not evaluated	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations.
HMG-CoA reductase inhibitors: Atorvastatin ^a	↑Atorvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed atorvastatin 20 mg/day.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents.
Inhaled beta-agonist:	↑Salmeterol	Concurrent administration of salmeterol

Salmeterol		with LEXIVA is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Inhaled/nasal steroid: Fluticasone	LEXIVA: ↑Fluticasone LEXIVA/ritonavir: ↑Fluticasone	Use with caution. Consider alternatives to fluticasone, particularly for long-term use. May result in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone. Coadministration of fluticasone and LEXIVA/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
Narcotic analgesic: Methadone	↓Methadone	Data suggest that the interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms.
Oral contraceptives: Ethinyl estradiol/ norethindrone ^a	LEXIVA: ↓Amprenavir ↓Ethinyl estradiol LEXIVA/ritonavir: ↓Ethinyl estradiol	Alternative methods of non-hormonal contraception are recommended. May lead to loss of virologic response. ^a Increased risk of transaminase elevations. No data are available on the use of LEXIVA/ritonavir with other hormonal therapies, such as hormone replacement therapy (HRT) for postmenopausal women.
PDE5 inhibitors: Sildenafil, tadalafil,	↑Sildenafil ↑Tadalafil	May result in an increase in PDE5 inhibitor-associated adverse events,

<p>ildenafil</p>	<p>↑Vardenafil</p>	<p>including hypotension, syncope, visual disturbances, and priapism.</p> <p><u>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):</u></p> <ul style="list-style-type: none"> • Use of sildenafil (REVATIO) is contraindicated when used for the treatment of PAH [<i>see Contraindications (4)</i>]. • <u>The following dose adjustments are recommended for use of tadalafil (ADCIRCA[®]) with LEXIVA:</u> <p><u>Coadministration of ADCIRCA in patients on LEXIVA:</u> In patients receiving LEXIVA for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Coadministration of LEXIVA in patients on ADCIRCA:</u> Avoid use of ADCIRCA during the initiation of LEXIVA. Stop ADCIRCA at least 24 hours prior to starting LEXIVA. After at least one week following the initiation of LEXIVA, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Use of PDE5 inhibitors for erectile dysfunction:</u></p> <p>LEXIVA: Sildenafil: 25 mg every 48 hours. Tadalafil: no more than 10 mg every 72 hours. Vardenafil: no more than 2.5 mg every 24 hours.</p>
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		<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. Use with increased monitoring for adverse events.</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>

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

292 **8 USE IN SPECIFIC POPULATIONS**

293 **8.1 Pregnancy**

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

306 The mating and fertility of the F₁ generation born to female rats given fosamprenavir was
307 not different from control animals; however, fosamprenavir did cause a reduction in both pup
308 survival and body weights. Surviving F₁ female rats showed an increased time to successful
309 mating, an increased length of gestation, a reduced number of uterine implantation sites per litter,
310 and reduced gestational body weights compared with control animals. Systemic exposure

311 (AUC_{0-24 hr}) to amprenavir in the F₀ pregnant rats was approximately 2 times higher than
312 exposures in humans following administration of the MRHD of fosamprenavir alone or
313 approximately the same as those seen in humans following administration of the MRHD of
314 fosamprenavir in combination with ritonavir.

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

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

320 **8.3 Nursing Mothers**

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

327 **8.4 Pediatric Use**

328 The safety, pharmacokinetic profile, virologic, and immunologic responses of LEXIVA
329 with and without ritonavir were evaluated in protease inhibitor-naive and –experienced HIV-1–
330 infected pediatric subjects aged at least 4 weeks to less than 18 years and weighing at least 3 kg
331 in 3 open-label trials [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical*
332 *Studies (14.3)*]. Vomiting and neutropenia, were more frequent in pediatrics than in adults [*see*
333 *Adverse Reactions (6.1)*]. Other adverse events occurred with similar frequency in pediatric
334 subjects compared with adults.

335 Treatment with LEXIVA is not recommended in protease inhibitor-experienced pediatric
336 patients younger than 6 months. The pharmacokinetics, safety, tolerability, and efficacy of
337 LEXIVA in pediatric patients younger than 4 weeks have not been established [*see Clinical*
338 *Pharmacology (12.3)*]. Available pharmacokinetic and clinical data do not support once-daily
339 dosing of LEXIVA alone or in combination with ritonavir for any pediatrics or twice-daily
340 dosing without ritonavir in pediatric patients younger than 2 years [*see Clinical Pharmacology*
341 *(12.3), Clinical Studies (14.3)*]. See *Dosage and Administration (2.2)* for dosing
342 recommendations for pediatric patients.

343 **8.5 Geriatric Use**

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

348 **8.6 Hepatic Impairment**

349 Amprenavir is principally metabolized by the liver; therefore, caution should be exercised
350 when administering LEXIVA to patients with hepatic impairment because amprenavir

351 concentrations may be increased [see *Clinical Pharmacology (12.3)*]. Patients with impaired
352 hepatic function receiving LEXIVA with or without concurrent ritonavir require dose reduction
353 [see *Dosage and Administration (2.3)*].

354 There are no data to support dosing recommendations for pediatric subjects with hepatic
355 impairment.

356 10 OVERDOSAGE

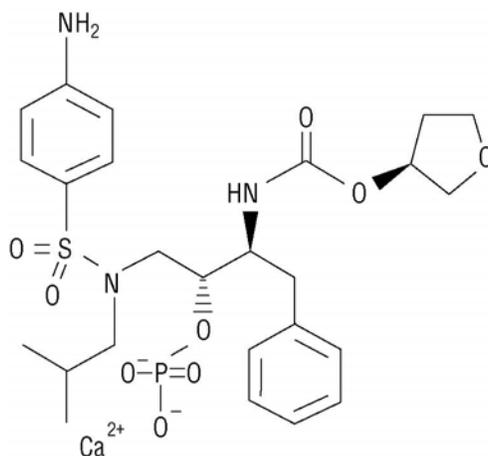
357 In a healthy volunteer repeat-dose pharmacokinetic study evaluating high-dose
358 combinations of LEXIVA plus ritonavir, an increased frequency of Grade 2/3 ALT elevations
359 (greater than 2.5 x ULN) was observed with LEXIVA 1,400 mg twice daily plus ritonavir
360 200 mg twice daily (4 of 25 subjects). Concurrent Grade 1/2 elevations in AST (greater than
361 1.25 x ULN) were noted in 3 of these 4 subjects. These transaminase elevations resolved
362 following discontinuation of dosing.

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

366 11 DESCRIPTION

367 LEXIVA (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of HIV
368 protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-
369 [[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonoxy) propylcarbamate
370 monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*)
371 configuration. It has a molecular formula of C₂₅H₃₄CaN₃O₉PS and a molecular weight of 623.7.
372 It has the following structural formula:

373



374

375

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

378 LEXIVA Tablets are available for oral administration in a strength of 700 mg of
379 fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir).

380 Each 700 mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose
381 sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet
382 film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and
383 triacetin.

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

390 **12 CLINICAL PHARMACOLOGY**

391 **12.1 Mechanism of Action**

392 Fosamprenavir is an antiviral agent [see *Microbiology (12.4)*].

393 **12.3 Pharmacokinetics**

394 The pharmacokinetic properties of amprenavir after administration of LEXIVA, with or
395 without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-1-infected
396 subjects; no substantial differences in steady-state amprenavir concentrations were observed
397 between the 2 populations.

398 The pharmacokinetic parameters of amprenavir after administration of LEXIVA (with
399 and without concomitant ritonavir) are shown in Table 8.

400

401 **Table 8. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
402 **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)

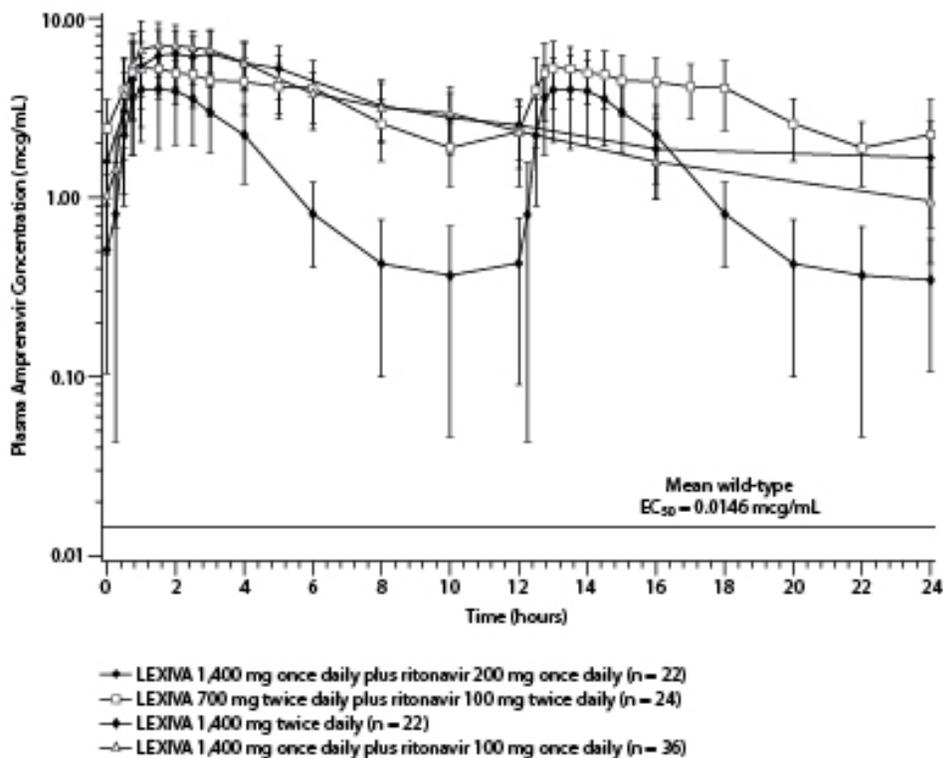
403 ^aData shown are median (range).

404

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

407

408 **Figure 1. Mean (\pm SD) Steady-State Plasma Amprenavir Concentrations**
 409 **and Mean EC₅₀ Values Against HIV from Protease Inhibitor-Naive**
 410 **Subjects (in the Absence of Human Serum)**



411
412

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

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

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

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

429 **Distribution:** In vitro, amprenavir is approximately 90% bound to plasma proteins,
430 primarily to alpha₁-acid glycoprotein. In vitro, concentration-dependent binding was observed
431 over the concentration range of 1 to 10 mcg per mL, with decreased binding at higher
432 concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as
433 amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher
434 concentrations.

435 **Metabolism:** After oral administration, fosamprenavir is rapidly and almost completely
436 hydrolyzed to amprenavir and inorganic phosphate prior to reaching the systemic circulation.
437 This occurs in the gut epithelium during absorption. Amprenavir is metabolized in the liver by
438 the CYP3A4 enzyme system. The 2 major metabolites result from oxidation of the
439 tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been
440 identified as minor metabolites in urine and feces.

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

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

448 **Special Populations: Hepatic Impairment:** The pharmacokinetics of amprenavir have
449 been studied after the administration of LEXIVA in combination with ritonavir to adult HIV-1–
450 infected subjects with mild, moderate, and severe hepatic impairment. Following 2 weeks of
451 dosing with LEXIVA plus ritonavir, the AUC of amprenavir was increased by approximately
452 22% in subjects with mild hepatic impairment, by approximately 70% in subjects with moderate
453 hepatic impairment, and by approximately 80% in subjects with severe hepatic impairment
454 compared with HIV-1–infected subjects with normal hepatic function. Protein binding of
455 amprenavir was decreased in subjects with hepatic impairment. The unbound fraction at 2 hours
456 (approximate C_{max}) ranged between a decrease of -7% to an increase of 57% while the unbound
457 fraction at the end of the dosing interval (C_{min}) increased from 50% to 102% [*see Dosage and*
458 *Administration (2.3)*].

459 The pharmacokinetics of amprenavir have been studied after administration of
460 amprenavir given as AGENERASE[®] Capsules to adult subjects with hepatic impairment.
461 Following administration of a single 600-mg oral dose, the AUC of amprenavir was increased by
462 approximately 2.5-fold in subjects with moderate cirrhosis and by approximately 4.5-fold in
463 subjects with severe cirrhosis compared with healthy volunteers [*see Dosage and Administration*
464 *(2.3)*].

465 **Renal Impairment:** The impact of renal impairment on amprenavir elimination in
466 adults has not been studied. The renal elimination of unchanged amprenavir represents
467 approximately 1% of the administered dose; therefore, renal impairment is not expected to
468 significantly impact the elimination of amprenavir.

469 *Pediatric Patients:* The pharmacokinetics of amprenavir following administration of
470 LEXIVA Oral Suspension and LEXIVA Tablets, with or without ritonavir, have been studied in
471 a total of 212 HIV-1–infected pediatric subjects enrolled in 3 trials. LEXIVA without ritonavir
472 was administered as 30 or 40 mg per kg twice daily to children aged 2 to 5 years. LEXIVA with
473 ritonavir was administered as LEXIVA 30 mg per kg plus ritonavir 6 mg per kg once daily to
474 children aged 2 to 18 years and as LEXIVA 18 to 60 mg per kg plus ritonavir 3 to 10 mg per kg
475 twice daily to children aged at least 4 weeks to 18 years; body weights ranged from 3 to 103 kg.

476 Amprenavir apparent clearance decreased with increasing weight. Weight-adjusted
477 apparent clearance was higher in children younger than 4 years, suggesting that younger children
478 require higher mg per kg dosing of LEXIVA.

479 The pharmacokinetics of LEXIVA Oral Suspension in protease inhibitor-naive infants
480 younger than 6 months (n = 9) receiving LEXIVA 45 mg per kg plus ritonavir 10 mg per kg
481 twice daily generally demonstrated lower AUC₁₂ and C_{min} than adults receiving twice-daily
482 LEXIVA 700 mg plus ritonavir 100 mg, the dose recommended for protease-experienced adults.
483 The mean steady-state amprenavir AUC₁₂, C_{max}, and C_{min} were 26.6 mcg•hour per mL, 6.25 mcg
484 per mL, and 0.86 mcg per mL, respectively. These data do not support twice-daily dosing of
485 LEXIVA alone or in combination with ritonavir in protease inhibitor-experienced patients
486 younger than 6 months. Because of expected low amprenavir exposure and a requirement for
487 large volume of drug, twice-daily dosing of LEXIVA alone (without ritonavir) in pediatric
488 subjects younger than 2 years was not studied.

489 Pharmacokinetic parameters for LEXIVA administered with food and with ritonavir in
490 this patient population at the recommended weight-band–based dosage regimens are provided in
491 Table 9.

492

493 **Table 9. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
 494 **Parameters by Weight in Pediatric and Adolescent Subjects Aged at Least 4 Weeks to 18**
 495 **Years Receiving LEXIVA With Ritonavir**

Weight	Recommended Dosage Regimen	C _{max}		AUC ₂₄		C _{min}	
		n	(mcg/mL)	n	(mcg•hr/mL)	n	(mcg/mL)
<11 kg	LEXIVA 45 mg/kg plus Ritonavir 7 mg/kg b.i.d	12	6.00 (3.88, 9.29)	12	57.3 (34.1, 96.2)	27	1.65 (1.22, 2.24)
11 kg - <15 kg	LEXIVA 30 mg/kg plus Ritonavir 3 mg/kg b.i.d	Not studied ^a					
15 kg - <20 kg	LEXIVA 23 mg/kg plus Ritonavir 3 mg/kg b.i.d.	5	9.54 (4.63, 19.7)	5	121 (54.2, 269)	9	3.56 (2.33, 5.43)
>20 kg - <39 kg	LEXIVA 18 mg/kg plus Ritonavir 3 mg/kg b.i.d.	13	6.24 (5.01, 7.77)	12	97.9 (77.0, 124)	23	2.54 (2.11, 3.06)
≥39 kg	LEXIVA 700 mg plus Ritonavir 100 mg b.i.d.	15	5.03 (4.04, 6.26)	15	72.3 (59.6, 87.6)	42	1.98 (1.72, 2.29)

496 ^a Recommended dose for pediatric subjects weighing 11 kg to less than 15 kg is based on
 497 population pharmacokinetic analysis.
 498

499 Subjects aged 2 to less than 6 years receiving LEXIVA 30 mg per kg twice daily without
 500 ritonavir achieved geometric mean (95% CI) amprenavir C_{max} (n = 9), AUC₁₂ (n = 9), and C_{min}
 501 (n = 19) of 7.15 (5.05, 10.1), 22.3 (15.3, 32.6), and 0.513 (0.384, 0.686), respectively.

502 **Geriatric Patients:** The pharmacokinetics of amprenavir after administration of
 503 LEXIVA to patients older than 65 years have not been studied [see *Use in Specific Populations*
 504 (8.5)].

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

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

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

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

517 Drug interaction trials were performed with LEXIVA and other drugs likely to be
 518 coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects
 519 of coadministration on AUC, C_{max}, and C_{min} values are summarized in Table 10 (effect of other
 520 drugs on amprenavir) and Table 12 (effect of LEXIVA on other drugs). In addition, since

521 LEXIVA delivers comparable amprenavir plasma concentrations as AGENERASE, drug
522 interaction data derived from trials with AGENERASE are provided in Tables 11 and 13. For
523 information regarding clinical recommendations, *[see Drug Interactions (7)]*.
524

525 **Table 10. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 526 **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/ norethindrone 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)
Maraviroc 300 mg b.i.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	14	↓34 (↓25 to ↓41)	↓35 (↓29 to ↓41)	↓36 (↓27 to ↓43)
Maraviroc 300 mg q.d. for 10 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 20 days	14	↓29 (↓20 to ↓38)	↓30 (↓23 to ↓36)	↓15 (↓3 to ↓25)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	↔ ^c	↔ ^c	↔ ^c
Nevirapine 200 mg b.i.d. for 2 weeks ^f	1,400 mg b.i.d. for 2 weeks	17	↓25 (↓37 to ↓10)	↓33 (↓45 to ↓20)	↓35 (↓50 to ↓15)
Nevirapine 200 mg b.i.d. for 2 weeks ^f	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↔	↓11 (↓23 to ↑3)	↓19 (↓32 to ↓4)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	13	↔	↑20 (↑8 to ↑34)	↑19 (↑6 to ↑33)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg b.i.d. for 14 days (fasted)	14	↓27 (↓46 to ↔)	↓36 (↓53 to ↓13)	↓43 ^g (↓59 to ↓21)
	1,400 mg b.i.d. for 14 days ^h	14	↓15 (↓27 to ↓1)	↓17 (↓27 to ↓6)	↓32 ^g (↓53 to ↓1)
	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days (fasted)	14	↓14 (↓39 to ↑20)	↓17 (↓38 to ↑12)	↓20 ^g (↓45 to ↑17)

	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days ^h	12	↓25 (↓42 to ↓2)	↓25 (↓44 to ↔)	↓33 ^g (↓52 to ↓7)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days (fasted)	13	↓18 (↓34 to ↔)	↓24 (↓41 to ↔)	↓50 ^g (↓64 to ↓31)
	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days ^h	14	↑27 (↓1 to ↑62)	↑13 (↓7 to ↑38)	↓17 ^g (↓45 to ↑26)
Ranitidine 300 mg single dose (administered 1 hour before fosamprenavir)	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	↔ (↓19 to ↑21)
Rifabutin 150 mg q.o.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↑36 ^c (↑18 to ↑55)	↑35 ^c (↑17 to ↑56)	↑17 ^c (↓1 to ↑39)
Telaprevir 750 mg q. 8 hr for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	18	↓35 (↓30 to ↓41)	↓47 (↓42 to ↓51)	↓56 (↓50 to ↓60)
Telaprevir 1,125 mg q. 12 hr for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 24 days	17	↓40 ⁱ (↓33 to ↓45)	↓49 ⁱ (↓45 to ↓53)	↓58 ⁱ (↓53 to ↓63)
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	↔ ^j
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	↔ ^j

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

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

530 ^c Compared with historical control.

531 ^d Subjects were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period
532 with both ketoconazole and LEXIVA/ritonavir.
533 ^e Compared with LEXIVA 700 mg/ritonavir 100 mg b.i.d. for 2 weeks.
534 ^f Subjects were receiving nevirapine for at least 12 weeks prior to study.
535 ^g C_{last} (C_{12 hr} or C_{24 hr}).
536 ^h Doses of LEXIVA and raltegravir were given with food on pharmacokinetic sampling days
537 and without regard to food all other days.
538 ⁱ N = 18 for C_{min}.
539 ^j Compared with parallel control group.
540 ↑= Increase; ↓= Decrease; ↔ = No change (↑ or ↓ less than or equal to 10%), NA = Not
541 applicable.
542

543 **Table 11. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 544 **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

545 ^a Compared with parallel control group.

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

547 ^c Compared with historical data.

548 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ less than 10%); NA = C_{min} not calculated for
549 single-dose study.
550

551 **Table 12. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
 552 **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)
Maraviroc 300 mg b.i.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	14	↑52 (↑27 to ↑82)	↑149 (↑119 to ↑182)	↑374 (↑303 to ↑457)

Maraviroc 300 mg q.d. for 10 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 20 days	14	↑45 (↑20 to ↑74)	↑126 (↑99 to ↑158)	↑80 (↑53 to ↑113)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	R-Methadone (active)		
			↓21 ^g (↓30 to ↓12)	↓18 ^g (↓27 to ↓8)	↓11 ^g (↓21 to ↑1)
			S-Methadone (inactive)		
			↓43 ^g (↓49 to ↓37)	↓43 ^g (↓50 to ↓36)	↓41 ^g (↓49 to ↓31)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	1,400 mg b.i.d. for 2 weeks	17	↑25 (↑14 to ↑37)	↑29 (↑19 to ↑40)	↑34 (↑20 to ↑49)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↑13 (↑3 to ↑24)	↑14 (↑5 to ↑24)	↑22 (↑9 to ↑35)
Norethindrone ^c 0.5 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓38 (↓32 to ↓44)	↓34 (↓30 to ↓37)	↓26 (↓20 to ↓32)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	14	↓20 (↓12 to ↓27)	↓22 (↓17 to ↓27)	↓29 (↓23 to ↓34)
Rifabutin 150 mg every other day for 2 weeks ⁱ (25-O-desacetylriofabutin metabolite)	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↓14 (↓28 to ↑4)	↔	↑28 (↑12 to ↑46)
Rifabutin + 25-O- desacetylriofabutin metabolite			↑579 (↑479 to ↑698)	↑1,120 (↑965 to ↑1,300)	↑2,510 (↑1,910 to ↑3,300)
			NA	↑64 (↑46 to ↑84)	NA
Rosuvastatin 10 mg single dose	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 7 days		(↑45)	(↑8)	NA

Telaprevir 750 mg q. 8 hr for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	18	↓33 (↓29 to ↓37)	↓32 (↓28 to ↓37)	↓30 (↓23 to ↓36)
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- 553 ^a Concomitant medication is also shown in this column where appropriate.
- 554 ^b Comparison arm of atazanavir 300 mg q.d. plus ritonavir 100 mg q.d. for 10 days.
- 555 ^c Administered as a combination oral contraceptive tablet: ethinyl estradiol
556 0.035 mg/norethindrone 0.5 mg.
- 557 ^d Subjects were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period
558 with both ketoconazole and LEXIVA/ritonavir.
- 559 ^e Data represent lopinavir concentrations.
- 560 ^f Compared with lopinavir 400 mg/ritonavir 100 mg b.i.d. for 2 weeks.
- 561 ^g Dose normalized to methadone 100 mg. The unbound concentration of the active moiety,
562 R-methadone, was unchanged.
- 563 ^h Subjects were receiving nevirapine for at least 12 weeks prior to study.
- 564 ⁱ Comparison arm of rifabutin 300 mg q.d. for 2 weeks. AUC is AUC_(0-48 hr).
- 565 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ less than 10%); ND = Interaction cannot be
566 determined as C_{min} was below the lower limit of quantitation.
- 567

568 **Table 13. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in**
569 **the 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	1,200 mg b.i.d.	16	R-Methadone (active)		

44 to 100 mg q.d. for >30 days	for 10 days		↓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

570 ^a Compared with historical data.

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

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

575

576 12.4 Microbiology

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

582 Antiviral Activity: Fosamprenavir has little or no antiviral activity in cell culture. The
583 antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically
584 infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes
585 in cell culture. The 50% effective concentration (EC₅₀) of amprenavir ranged from 0.012 to
586 0.08 microM in acutely infected cells and was 0.41 microM in chronically infected cells
587 (1 microM = 0.50 mcg per mL). The median EC₅₀ value of amprenavir against HIV-1 isolates
588 from clades A to G was 0.00095 microM in peripheral blood mononuclear cells (PBMCs).
589 Similarly, the EC₅₀ values for amprenavir against monocytes/macrophage tropic HIV-1 isolates
590 (clade B) ranged from 0.003 to 0.075 microM in monocyte/macrophage cultures. The EC₅₀

591 values of amprenavir against HIV-2 isolates grown in PBMCs were higher than those for HIV-1
592 isolates, and ranged from 0.003 to 0.11 microM. Amprenavir exhibited synergistic anti-HIV-1
593 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir,
594 didanosine, lamivudine, stavudine, tenofovir, and zidovudine; the non-nucleoside reverse
595 transcriptase inhibitors (NNRTIs) delavirdine and efavirenz; and the protease inhibitors
596 atazanavir and saquinavir. Amprenavir exhibited additive anti-HIV-1 activity in combination
597 with the NNRTI nevirapine, the protease inhibitors indinavir, lopinavir, nelfinavir, and ritonavir;
598 and the fusion inhibitor enfuvirtide. These drug combinations have not been adequately studied
599 in humans.

600 **Resistance:** HIV-1 isolates with decreased susceptibility to amprenavir have been
601 selected in cell culture and obtained from subjects treated with fosamprenavir. Genotypic
602 analysis of isolates from treatment-naïve subjects failing amprenavir-containing regimens
603 showed substitutions in the HIV-1 protease gene resulting in amino acid substitutions primarily
604 at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as substitutions in the p7/p1
605 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. Some of these amprenavir
606 resistance-associated substitutions have also been detected in HIV-1 isolates from
607 antiretroviral-naïve subjects treated with LEXIVA. Of the 488 antiretroviral-naïve subjects
608 treated with LEXIVA 1,400 mg twice daily or LEXIVA 1,400 mg plus ritonavir 200 mg once
609 daily in Trials APV30001 and APV30002, respectively, 61 subjects (29 receiving LEXIVA and
610 32 receiving LEXIVA/ritonavir) with virologic failure (plasma HIV-1 RNA greater than
611 1,000 copies per mL on 2 occasions on or after Week 12) were genotyped. Five of the
612 29 antiretroviral-naïve subjects (17%) receiving LEXIVA without ritonavir in Trial APV30001
613 had evidence of genotypic resistance to amprenavir: I54L/M (n = 2), I54L + L33F (n = 1),
614 V32I + I47V (n = 1), and M46I + I47V (n = 1). No amprenavir resistance-associated
615 substitutions were detected in antiretroviral-naïve subjects treated with LEXIVA/ritonavir for
616 48 weeks in Trial APV30002. However, the M46I and I50V substitutions were detected in
617 isolates from 1 virologic failure subject receiving LEXIVA/ritonavir once daily at Week 160
618 (HIV-1 RNA greater than 500 copies per mL). Upon retrospective analysis of stored samples
619 using an ultrasensitive assay, these resistant substitutions were traced back to Week 84
620 (76 weeks prior to clinical virologic failure).

621 **Cross-Resistance:** Varying degrees of cross-resistance among HIV-1 protease
622 inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1
623 RNA level less than 400 copies per mL) and protease inhibitor-resistance substitutions detected
624 in baseline HIV-1 isolates from protease inhibitor-experienced subjects receiving
625 LEXIVA/ritonavir twice daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in Trial
626 APV30003 is shown in Table 14. The majority of subjects had previously received either one
627 (47%) or 2 protease inhibitors (36%), most commonly nelfinavir (57%) and indinavir (53%). Out
628 of 102 subjects with baseline phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (n = 55)
629 had resistance to at least one protease inhibitor, with 98% (n = 54) of those having resistance to
630 nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60%

631 (n = 58) had resistance to at least one protease inhibitor, with 97% (n = 56) of those having
632 resistance to nelfinavir.

633
634 **Table 14. Responders at Trial Week 48 by Presence of Baseline Protease Inhibitor**
635 **Resistance-Associated Substitutions^a**

Protease Inhibitor Resistance-Associated Substitutions ^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%

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

637 ^bMost subjects had greater than 1 protease inhibitor resistance-associated substitution at baseline.

638
639 The virologic response based upon baseline phenotype was assessed. Baseline isolates
640 from protease inhibitor-experienced subjects responding to LEXIVA/ritonavir twice daily had a
641 median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of
642 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a
643 median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient
644 population, these data do not constitute definitive clinical susceptibility break points. Additional
645 data are needed to determine clinically relevant break points for LEXIVA.

646 Isolates from 15 of the 20 subjects receiving twice-daily LEXIVA/ritonavir up to
647 Week 48 and experiencing virologic failure/ongoing replication were subjected to genotypic
648 analysis. The following amprenavir resistance-associated substitutions were found either alone or
649 in combination: V32I, M46I/L, I47V, I50V, I54L/M, and I84V. Isolates from 4 of the 16 subjects
650 continuing to receive twice-daily LEXIVA/ritonavir up to Week 96 who experienced virologic
651 failure underwent genotypic analysis. Isolates from 2 subjects contained amprenavir
652 resistance-associated substitutions: V32I, M46I, and I47V in 1 isolate and I84V in the other.

653 **13 NONCLINICAL TOXICOLOGY**

654 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

655 In long-term carcinogenicity studies, fosamprenavir was administered orally for up to
656 104 weeks at doses of 250, 400, or 600 mg per kg per day in mice and at doses of 300, 825, or

657 2,250 mg per kg per day in rats. Exposures at these doses were 0.3- to 0.7-fold (mice) and 0.7- to
658 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to
659 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of
660 fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were
661 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir
662 plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and
663 hepatocellular carcinomas at all doses in male mice and at 600 mg per kg per day in female mice,
664 and in hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and
665 at 835 mg per kg per day and 2,250 mg per kg per day in female rats. The relevance of the
666 hepatocellular findings in the rodents for humans is uncertain. Repeat dose studies with
667 fosamprenavir in rats produced effects consistent with enzyme induction, which predisposes rats,
668 but not humans, to thyroid neoplasms. In addition, in rats only there was an increase in
669 interstitial cell hyperplasia at 825 mg per kg per day and 2,250 mg per kg per day, and an
670 increase in uterine endometrial adenocarcinoma at 2,250 mg per kg per day. The incidence of
671 endometrial findings was slightly increased over concurrent controls, but was within background
672 range for female rats. The relevance of the uterine endometrial adenocarcinoma findings in rats
673 for humans is uncertain.

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

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

685 **14 CLINICAL STUDIES**

686 **14.1 Therapy-Naive Adult Trials**

687 APV30001: A randomized, open-label trial evaluated treatment with LEXIVA Tablets
688 (1,400 mg twice daily) versus nelfinavir (1,250 mg twice daily) in 249 antiretroviral
689 treatment-naive subjects. Both groups of subjects also received abacavir (300 mg twice daily)
690 and lamivudine (150 mg twice daily).

691 The mean age of the subjects in this study was 37 years (range: 17 to 70 years); 69% of
692 the subjects were male, 20% were CDC Class C (AIDS), 24% were Caucasian, 32% were black,
693 and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells per mm^3 (range:
694 2 to 1,136 cells per mm^3 ; 18% of subjects had a CD4+ cell count of less than 50 cells per mm^3
695 and 30% were in the range of 50 to less than 200 cells per mm^3). Baseline median HIV-1 RNA

696 was 4.83 log₁₀ copies per mL (range: 1.69 to 7.41 log₁₀ copies per mL; 45% of subjects had
 697 greater than 100,000 copies per mL).

698 The outcomes of randomized treatment are provided in Table 15.
 699

700 **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%

701 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per
 702 mL (less than 50 copies per mL) through Week 48 (Roche AMPLICOR HIV-1
 703 MONITOR Assay Version 1.5).

704 ^b Includes consent withdrawn, lost to follow up, protocol violations, those with
 705 missing data, and other reasons.
 706

707 Treatment response by viral load strata is shown in Table 16.
 708

709 **Table 16. Proportions of Responders Through Week 48 by Screening Viral Load**
 710 **(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

711
 712 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
 713 were 201 cells per mm³ in the group receiving LEXIVA and 216 cells per mm³ in the nelfinavir
 714 group.

715 APV30002: A randomized, open-label trial evaluated treatment with LEXIVA Tablets
 716 (1,400 mg once daily) plus ritonavir (200 mg once daily) versus nelfinavir (1,250 mg twice
 717 daily) in 649 treatment-naïve subjects. Both treatment groups also received abacavir (300 mg
 718 twice daily) and lamivudine (150 mg twice daily).

719 The mean age of the subjects in this study was 37 years (range: 18 to 69 years); 73% of
 720 the subjects were male, 22% were CDC Class C, 53% were Caucasian, 36% were black, and 8%
 721 were Hispanic. At baseline, the median CD4+ cell count was 170 cells per mm³ (range: 1 to
 722 1,055 cells per mm³; 20% of subjects had a CD4+ cell count of less than 50 cells per mm³ and
 723 35% were in the range of 50 to less than 200 cells per mm³). Baseline median HIV-1 RNA was
 724 4.81 log₁₀ copies per mL (range: 2.65 to 7.29 log₁₀ copies per mL; 43% of subjects had greater
 725 than 100,000 copies per mL).

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

727

728 **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%

729 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per
 730 mL (less than 50 copies per mL) through Week 48 (Roche AMPLICOR HIV-1
 731 MONITOR Assay Version 1.5).

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

734

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

736

737 **Table 18. Proportions of Responders Through Week 48 by Screening Viral Load**
 738 **(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

739

740 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts
 741 were 203 cells per mm³ in the group receiving LEXIVA and 207 cells per mm³ in the nelfinavir
 742 group.

743 **14.2 Protease Inhibitor-Experienced Adult Trials**

744 APV30003: A randomized, open-label, multicenter trial evaluated 2 different regimens
745 of LEXIVA plus ritonavir (LEXIVA Tablets 700 mg twice daily plus ritonavir 100 mg twice
746 daily or LEXIVA Tablets 1,400 mg once daily plus ritonavir 200 mg once daily) versus
747 lopinavir/ritonavir (400 mg/100 mg twice daily) in 315 subjects who had experienced virologic
748 failure to 1 or 2 prior protease inhibitor-containing regimens.

749 The mean age of the subjects in this study was 42 years (range: 24 to 72 years); 85%
750 were male, 33% were CDC Class C, 67% were Caucasian, 24% were black, and 9% were
751 Hispanic. The median CD4+ cell count at baseline was 263 cells per mm³ (range: 2 to 1,171 cells
752 per mm³). Baseline median plasma HIV-1 RNA level was 4.14 log₁₀ copies per mL (range: 1.69
753 to 6.41 log₁₀ copies per mL).

754 The median durations of prior exposure to NRTIs were 257 weeks for subjects receiving
755 LEXIVA/ritonavir twice daily (79% had greater than or equal to 3 prior NRTIs) and 210 weeks
756 for subjects receiving lopinavir/ritonavir (64% had greater than or equal to 3 prior NRTIs). The
757 median durations of prior exposure to protease inhibitors were 149 weeks for subjects receiving
758 LEXIVA/ritonavir twice daily (49% received greater than or equal to 2 prior protease inhibitors)
759 and 130 weeks for subjects receiving lopinavir/ritonavir (40% received greater than or equal to
760 2 prior protease inhibitors).

761 The time-averaged changes in plasma HIV-1 RNA from baseline (AAUCMB) at
762 48 weeks (the endpoint on which the study was powered) were -1.4 log₁₀ copies per mL for
763 twice-daily LEXIVA/ritonavir and -1.67 log₁₀ copies per mL for the lopinavir/ritonavir group.

764 The proportions of subjects who achieved and maintained confirmed HIV-1 RNA less
765 than 400 copies per mL (secondary efficacy endpoint) were 58% with twice-daily
766 LEXIVA/ritonavir and 61% with lopinavir/ritonavir (95% CI for the difference: -16.6, 10.1). The
767 proportions of subjects with HIV-1 RNA less than 50 copies per mL with twice-daily
768 LEXIVA/ritonavir and with lopinavir/ritonavir were 46% and 50%, respectively (95% CI for the
769 difference: -18.3, 8.9). The proportions of subjects who were virologic failures were 29% with
770 twice-daily LEXIVA/ritonavir and 27% with lopinavir/ritonavir.

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

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

776 This trial was not large enough to reach a definitive conclusion that LEXIVA/ritonavir
777 and lopinavir/ritonavir are clinically equivalent.

778 Once-daily administration of LEXIVA plus ritonavir is not recommended for protease
779 inhibitor-experienced patients. Through Week 48, 50% and 37% of subjects receiving LEXIVA
780 1,400 mg plus ritonavir 200 mg once daily had plasma HIV-1 RNA less than 400 copies per mL
781 and less than 50 copies per mL, respectively.

782 **14.3 Pediatric Trials**

783 Three open-label trials in pediatric subjects aged at least 4 weeks to 18 years were
784 conducted. In one trial (APV29005), twice-daily dosing regimens (LEXIVA with or without
785 ritonavir) were evaluated in combination with other antiretroviral agents in pediatric subjects
786 aged 2 to 18 years. In a second trial (APV20002), twice-daily dosing regimens (LEXIVA with
787 ritonavir) were evaluated in combination with other antiretroviral agents in pediatric subjects
788 aged at least 4 weeks to less than 2 years. A third trial (APV20003) evaluated once-daily dosing
789 of LEXIVA with ritonavir; the pharmacokinetic data from this trial did not support a once-daily
790 dosing regimen in any pediatric patient population.

791 APV29005: LEXIVA: Twenty (18 therapy-naive and 2 therapy-experienced) pediatric
792 subjects received LEXIVA Oral Suspension without ritonavir twice daily. At Week 24, 65%
793 (13/20) achieved HIV-1 RNA less than 400 copies per mL, and the median increase from
794 baseline in CD4+ cell count was 350 cells per mm³.

795 LEXIVA plus Ritonavir: Forty-nine protease inhibitor-naive and 40 protease
796 inhibitor-experienced pediatric subjects received LEXIVA Oral Suspension or Tablets with
797 ritonavir twice daily. At Week 24, 71% of protease inhibitor-naive (35/49) and 55% of protease
798 inhibitor-experienced (22/40) subjects achieved HIV-1 RNA less than 400 copies per mL;
799 median increases from baseline in CD4+ cell counts were 184 cells per mm³ and 150 cells per
800 mm³ in protease inhibitor-naive and experienced subjects, respectively.

801 APV20002: Fifty-four pediatric subjects (49 protease inhibitor-naive and 5 protease
802 inhibitor-experienced) received LEXIVA Oral Suspension with ritonavir twice daily. At Week
803 24, 72% of subjects achieved HIV-1 RNA less than 400 copies per mL. The median increases
804 from baseline in CD4+ cell counts were 400 cells per mm³ in subjects aged at least 4 weeks to
805 less than 6 months and 278 cells per mm³ in subjects aged 6 months to 2 years.

806 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

810 Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C
811 (59° to 86°F) (see USP Controlled Room Temperature). Keep container tightly closed.

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

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

816 This product does not require reconstitution.

817 Store in refrigerator or at room temperature (5° to 30°C; 41° to 86°F). Shake vigorously
818 before using. Do not freeze.

819 **17 PATIENT COUNSELING INFORMATION**

820 *See FDA-approved Patient Labeling (Patient Information)*

821 **17.1 Drug Interactions**

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

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

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

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

833 **17.2 Sulfa Allergy**

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

836 **17.3 Redistribution/Accumulation of Body Fat**

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

840 **17.4 Information About Therapy With LEXIVA**

841 LEXIVA is not a cure for HIV-1 infection and patients may continue to experience
842 illnesses associated with HIV-1 infection, including opportunistic infections. Patients should
843 remain under the care of a physician when using LEXIVA.

844 Patients should be advised to avoid doing things that can spread HIV-1 infection to
845 others.

- 846 • **Do not share needles or other injection equipment.**
- 847 • **Do not share personal items that can have blood or body fluids on them, like**
848 **toothbrushes and razor blades.**
- 849 • **Do not have any kind of sex without protection.** Always practice safe sex by using a latex
850 or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions,
851 or blood.
- 852 • **Do not breastfeed.** We do not know if LEXIVA can be passed to your baby in your breast
853 milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed
854 because HIV-1 can be passed to the baby in the breast milk.

855 Patients should be told that sustained decreases in plasma HIV-1 RNA have been
856 associated with a reduced risk of progression to AIDS and death. Patients should be advised to
857 take LEXIVA every day as prescribed. LEXIVA must always be used in combination with other
858 antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting
859 their physician. If a dose is missed, patients should take the dose as soon as possible and then
860 return to their normal schedule. However, if a dose is skipped, the patient should not double the
861 next dose.

862 **17.5 Oral Suspension**

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

865
866 LEXIVA and AGENERASE are registered trademarks of ViiV Healthcare.

867
868 The brands listed are trademarks of their respective owners and are not trademarks of ViiV
869 Healthcare. The makers of these brands are not affiliated with and do not endorse ViiV
870 Healthcare or its products.

871
872
873 Manufactured for:



ViiV Healthcare
Research Triangle Park, NC 27709



Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

874
875 by:



GlaxoSmithKline

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877 GlaxoSmithKline
878 Research Triangle Park, NC 27709

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881
882 LXV:16PI

883
884 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT
885

886 **PATIENT INFORMATION**

887
888 **LEXIVA[®]** (lex-EE-vah)
889 **(fosamprenavir calcium)**
890 **Tablets**
891 **and**
892 **Oral Suspension**
893

894 **Important: LEXIVA can interact with other medicines and cause serious**
895 **side effects. It is important to know the medicines that should not be taken**
896 **with LEXIVA. See the section “Who should not take LEXIVA?”**
897

898 Read this Patient Information before you start taking LEXIVA and each time you get
899 a refill. There may be new information. This information does not take the place of
900 talking with your healthcare provider about your medical condition or treatment.
901

902 **What is LEXIVA?**

903 LEXIVA is a prescription anti-HIV medicine used with other anti-HIV medicines to
904 treat human immunodeficiency (HIV-1) infections in adults and children 4 weeks of
905 age and older. LEXIVA is a type of anti-HIV medicine called a protease inhibitor.
906 HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

907 When used with other anti-HIV medicines, LEXIVA may help:

- 908 1. Reduce the amount of HIV-1 in your blood. This is called “viral load”.
- 909 2. Increase the number of white blood cells called CD4 (T) cells, which help fight
910 off other infections. Reducing the amount of HIV-1 and increasing the CD4 (T)
911 cell count may improve your immune system. This may reduce your risk of
912 death or infections that can happen when your immune system is weak
913 (opportunistic infections).

914 It is not known if LEXIVA is safe and effective in children less than 4 weeks of age.

915 **LEXIVA does not cure HIV-1 infection or AIDS.** People taking LEXIVA may
916 develop infections or other conditions associated with HIV-1 infection, including
917 opportunistic infections (for example, pneumonia and herpes virus infections).

918 You should remain under the care of your healthcare provider when using LEXIVA.

919 Avoid doing things that can spread HIV-1 infection to others.

- 920 • **Do not share needles or other injection equipment.**
- 921 • **Do not share personal items that can have blood or body fluids on them,**
922 **like toothbrushes and razor blades.**
- 923 • **Do not have any kind of sex without protection.** Always practice safe sex
924 by using a latex or polyurethane condom to lower the chance of sexual contact
925 with semen, vaginal secretions, or blood.

926 Ask your healthcare provider if you have any questions on how to prevent passing
927 HIV to other people.
928

929 **Who should not take LEXIVA?**

930 **Do not take LEXIVA if you take any of the following medicines:**

- 931 • alfuzosin (UROXATRAL[®])
- 932 • flecainide (TAMBOCOR[™])
- 933 • propafenone (RYTHMOL SR[®])
- 934 • rifampin (RIFADIN[®], RIFAMATE[®], RIFATER[®], RIMACTANE[®])
- 935 • ergot including:
 - 936 • dihydroergotamine mesylate (D.H.E. 45[®], MIGRANAL[®])
 - 937 • ergotamine tartrate (CAFERGOT[®], MIGERGOT[®], ERGOMAR[®], MEDIHALER
 - 938 ERGOTAMINE[®])
 - 939 • methylergonovine (METHERGINE[®])
- 940 • St. John's wort (*Hypericum perforatum*)
- 941 • lovastatin (ADVICOR[®], ALTOPREV[®], MEVACOR[®])
- 942 • simvastatin (ZOCOR[®], VYTORIN[®], SIMCOR[®])
- 943 • pimozide (ORAP[®])
- 944 • delavirdine mesylate (RESCRIPTOR[®])
- 945 • sildenafil (REVATIO[®]), for treatment of pulmonary arterial hypertension
- 946 • triazolam (HALCION[®])

947 Serious problems can happen if you or your child take any of the medicines listed
 948 above with LEXIVA.

949 **Do not take LEXIVA if you are allergic** to AGENERASE[®] (amprenavir),
 950 fosamprenavir calcium, or any of the ingredients in LEXIVA. See the end of this
 951 leaflet for a complete list of ingredients in LEXIVA.

952

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

954 Before taking LEXIVA, tell your healthcare provider if you:

- 955 • are allergic to medicines that contain sulfa
- 956 • have liver problems, including hepatitis B or C
- 957 • have kidney problems
- 958 • have high blood sugar (diabetes)
- 959 • have hemophilia
- 960 • have any other medical condition
- 961 • are pregnant or plan to become pregnant. It is not known if LEXIVA will harm
 962 your unborn baby.

963 **Pregnancy Registry.** There is a pregnancy registry for women who take
 964 antiviral medicines during pregnancy. The purpose of the registry is to collect
 965 information about the health of you and your baby. Talk to your healthcare
 966 provider about how you can take part in this registry.

- 967 • **Do not breastfeed.** We do not know if LEXIVA can be passed to your baby in
 968 your breast milk and whether it could harm your baby. Also, mothers with HIV-1

969 should not breastfeed because HIV-1 can be passed to the baby in the breast
970 milk.

971 **Tell your healthcare provider about all prescription and non-prescription**
972 **medicines you take. Also tell your healthcare provider about any vitamins,**
973 **herbal supplements, and dietary supplements you are taking.**

974 Taking LEXIVA with certain other medicines may cause serious side effects. LEXIVA
975 may affect the way other medicines work, and other medicines may affect how
976 LEXIVA works.

977 Especially tell your healthcare provider if you take estrogen-based contraceptives
978 (birth control pills). LEXIVA may reduce effectiveness of estrogen-based
979 contraceptives. During treatment with LEXIVA, you should use a different
980 contraceptive method.

981 Know all the medicines that you take. Keep a list of them with you to show
982 healthcare providers and pharmacists when you get a new medicine.

983

984 **How should I take LEXIVA?**

985 • **Stay under the care of a healthcare provider while taking LEXIVA.**

986 • Take LEXIVA exactly as prescribed by your healthcare provider.

987 • Do not change your dose or stop taking LEXIVA without talking with your
988 healthcare provider.

989 • If your child is taking LEXIVA, your child's healthcare provider will decide the
990 right dose based on your child's weight.

991 • You can take LEXIVA Tablets with or without food.

992 • **Adults should take LEXIVA Oral Suspension without food.**

993 • **Children should take LEXIVA Oral Suspension with food.** If your child
994 vomits within 30 minutes after taking a dose of LEXIVA, the dose should be
995 repeated.

996 • Shake LEXIVA Oral Suspension well before each use.

997 • If you miss a dose of LEXIVA, take the next dose as soon as possible and then
998 take your next dose at the regular time. Do not double the next dose. If you take
999 too much LEXIVA, call your healthcare provider or go to the nearest hospital
1000 emergency room right away.

1001

1002 **What are the possible side effects of LEXIVA?**

1003 **LEXIVA may cause serious side effects including:**

- 1004 • **Severe skin rash.** LEXIVA may cause severe or life-threatening skin reactions
1005 or rash.
- 1006 **If you get a rash with any of the following symptoms, stop taking**
1007 **LEXIVA and call your healthcare provider or get medical help right**
1008 **away:**
- 1009 • hives or sores in your mouth, or your skin blisters and peels
 - 1010 • trouble swallowing or breathing
 - 1011 • swelling of your face, eyes, lips, tongue, or throat
- 1012 • **Liver problems.** Your healthcare provider should do blood tests before and
1013 during your treatment with LEXIVA to check your liver function. Some people
1014 with liver problems, including hepatitis B or C, may have an increased risk of
1015 developing worsening liver problem during treatment with LEXIVA.
- 1016 • **Diabetes and high blood sugar (hyperglycemia).** Some people who take
1017 protease inhibitors, including LEXIVA, can get high blood sugar, develop
1018 diabetes, or your diabetes can get worse. Tell your healthcare provider if you
1019 notice an increase in thirst or urinate often while taking LEXIVA.
- 1020 • **Changes in your immune system (Immune Reconstitution Syndrome)** can
1021 happen when you start taking HIV medicines. Your immune system may get
1022 stronger and begin to fight infections that have been hidden in your body for a
1023 long time. Call your healthcare provider right away if you start having new
1024 symptoms after starting your HIV medicine.
- 1025 • **Changes in body fat.** These changes can happen in people who take
1026 antiretroviral therapy. The changes may include an increased amount of fat in
1027 the upper back and neck (“buffalo hump”), breast, and around the back, chest,
1028 and stomach area. Loss of fat from the legs, arms, and face may also happen.
1029 The exact cause and long-term health effects of these conditions are not known.
- 1030 • **Changes in blood tests.** Some people have changes in blood tests while taking
1031 LEXIVA. These include increases seen in liver function tests, blood fat levels, and
1032 decreases in white blood cells. Your healthcare provider should do regular blood
1033 tests before and during your treatment with LEXIVA.
- 1034 • **Increased bleeding problems in some people with hemophilia.** Some
1035 people with hemophilia have increased bleeding with protease inhibitors,
1036 including LEXIVA.
- 1037 • **Kidney stones.** Some people have developed kidney stones while taking
1038 LEXIVA. Tell your healthcare provider right away if you develop signs or
1039 symptoms of kidney stones:
- 1040 • pain in your side
 - 1041 • blood in your urine
 - 1042 • pain when you urinate
- 1043 **The most common side effects of LEXIVA in adults include:**

- 1044 • nausea
- 1045 • vomiting
- 1046 • diarrhea
- 1047 • headache

1048 Vomiting is the most common side effect in children when taking LEXIVA.

1049 Tell your healthcare provider about any side effect that bothers you or that does
1050 not go away.

1051 These are not all the possible side effects of LEXIVA. For more information, ask
1052 your healthcare provider or pharmacist.

1053

1054 Call your doctor for medical advice about side effects. You may report side effects
1055 to FDA at 1-800-FDA-1088.

1056

1057 **How should I store LEXIVA?**

- 1058 • Store LEXIVA Tablets at room temperature between 68°F to 77°F (20°C to
1059 25°C).
- 1060 • Keep the bottle of LEXIVA Tablets tightly closed.
- 1061 • Store LEXIVA Oral Suspension between 41°F to 86°F (5°C to 30°C).
1062 Refrigeration of LEXIVA Oral Suspension may improve taste for some people.
- 1063 • Do not freeze.

1064 **Keep LEXIVA and all medicines out of the reach of children.**

1065

1066 **General information about LEXIVA**

1067 Medicines are sometimes prescribed for purposes other than those listed in a
1068 Patient Information leaflet. Do not use LEXIVA for a condition for which it was not
1069 prescribed. Do not give LEXIVA to other people, even if they have the same
1070 symptoms you have. It may harm them.

1071 This leaflet summarizes the most important information about LEXIVA. If you would
1072 like more information, talk with your healthcare provider. You can ask your
1073 pharmacist or healthcare provider for information about LEXIVA that is written for
1074 health professionals.

1075 For more information call 877-844-8872 or go to www.LEXIVA.com.

1076

1077 **What are the ingredients in LEXIVA?**

1078 **Tablets:**

1079 **Active ingredient:** fosamprenavir calcium

1080 **Inactive ingredients:** colloidal silicon dioxide, croscarmellose sodium, magnesium
1081 stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating
1082 contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and
1083 triacetin.

1084 **Oral Suspension:**

1085 **Active ingredient:** fosamprenavir calcium

1086 **Inactive ingredients:** artificial grape-bubblegum flavor, calcium chloride
1087 dihydrate, hypromellose, methylparaben, natural peppermint flavor, polysorbate
1088 80, propylene glycol, propylparaben, purified water, and sucralose.

1089

1090 This Patient Information has been approved by the U.S. Food and Drug
1091 Administration.

1092

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1094

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1096 of ViiV Healthcare. The makers of these brands are not affiliated with and do not
1097 endorse ViiV Healthcare or its products.

1098

1099

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1105

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