

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
Warnings and Precautions, Immune Reconstitution Syndrome (5.6)	02/2012

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 pediatric patients 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: 04/2012

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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 less than 6 months of age [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 2 years of age 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 of age [*see Clinical Pharmacology*
57 *(12.3)*].
- 58 • do not support twice-daily dosing of LEXIVA without ritonavir in pediatric patients younger
59 than 2 years of age [*see Clinical Pharmacology (12.3)*].

60 Other Dosing Considerations:

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

66 **2.3 Patients With Hepatic Impairment**

67 *See Clinical Pharmacology (12.3).*

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

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

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

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

82 **3 DOSAGE FORMS AND STRENGTHS**

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

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

87 **4 CONTRAINDICATIONS**

88 LEXIVA is contraindicated:

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

94

95 **Table 2. Drugs Contraindicated With LEXIVA (Information in the table applies to**
 96 **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.

97 ^a See *Clinical Pharmacology (12.3) Tables 10, 11, 12, or 13 for magnitude of interaction.*
 98

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

102 **5 WARNINGS AND PRECAUTIONS**

103 **5.1 Drug Interactions**

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

108 **5.2 Skin Reactions**

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

113 **5.3 Sulfa Allergy**

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

122 **5.4 Hepatic Toxicity**

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

129 **5.5 Diabetes/Hyperglycemia**

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

138 **5.6 Immune Reconstitution Syndrome**

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

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

148 **5.7 Fat Redistribution**

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

154 **5.8 Lipid Elevations**

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

159 **5.9 Hemolytic Anemia**

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

161 **5.10 Patients With Hemophilia**

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

166 **5.11 Nephrolithiasis**

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

171 **5.12 Resistance/Cross-Resistance**

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

176

177 **6 ADVERSE REACTIONS**

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

186 **6.1 Clinical Trials**

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

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

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

201

202 **Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater Than**
203 **or Equal to 2% of Antiretroviral-Naïve 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%

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

205

206 **Table 4. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater Than**
207 **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%

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

209

210 Skin rash (without regard to causality) occurred in approximately 19% of subjects treated
211 with LEXIVA in the pivotal efficacy trials. Rashes were usually maculopapular and of mild or
212 moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of
213 LEXIVA and had a median duration of 13 days. Skin rash led to discontinuation of LEXIVA in
214 less than 1% of subjects. In some subjects with mild or moderate rash, dosing with LEXIVA was

215 often continued without interruption; if interrupted, reintroduction of LEXIVA generally did not
 216 result in rash recurrence.

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

219
 220 **Table 5. Grade 3/4 Laboratory Abnormalities Reported in Greater Than or Equal to 2%**
 221 **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%

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

223 ^b Fasting specimens.

224 ULN = Upper limit of normal.

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

228
 229 **Table 6. Grade 3/4 Laboratory Abnormalities Reported in Greater Than or Equal to 2%**
 230 **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

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

232 ^b Fasting specimens.

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

234 ULN = Upper limit of normal.

235

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

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

246 The median duration of drug-related vomiting episodes in APV29005 was 1 day (range: 1 to
247 3 days), in APV20003 was 16 days (range: 1 to 38 days), and in APV20002 was 9 days (range: 4
248 to 13 days). Vomiting was treatment limiting in 4 pediatric subjects across all 3 trials.

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

253 **6.2 Postmarketing Experience**

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

259 **Cardiac Disorders:** Myocardial infarction.

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

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

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

263 **Urogenital:** Nephrolithiasis.

264 **7 DRUG INTERACTIONS**

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

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

268 **7.1 Cytochrome P450 Inhibitors and Inducers**

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

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

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

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

285 **7.2 Drugs That Should Not Be Coadministered With LEXIVA**

286 *See Contraindications (4).*

287 **7.3 Established and Other Potentially Significant Drug Interactions**

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

291

292 **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>HIV-Antiviral Agents</i>		
Non-nucleoside reverse transcriptase inhibitor: Efavirenz ^a	LEXIVA: ↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
	LEXIVA/ritonavir: ↓Amprenavir	An additional 100 mg/day (300 mg total) of ritonavir is recommended when

		efavirenz is administered with LEXIVA/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with LEXIVA plus ritonavir twice daily.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine ^a	LEXIVA: ↓Amprenavir ↑Nevirapine LEXIVA/ritonavir: ↓Amprenavir ↑Nevirapine	Coadministration of nevirapine and LEXIVA without ritonavir is not recommended. No dosage adjustment required when nevirapine is administered with LEXIVA/ritonavir twice daily. The combination of nevirapine administered with LEXIVA/ritonavir once-daily regimen has not been studied.
HIV protease inhibitor: Atazanavir ^a	LEXIVA: Interaction has not been evaluated. LEXIVA/ritonavir: ↓Atazanavir ↔Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Indinavir ^a , nelfinavir ^a	LEXIVA: ↑Amprenavir Effect on indinavir and nelfinavir is not well established. LEXIVA/ritonavir: Interaction has not been evaluated.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Lopinavir/ritonavir ^a	↓Amprenavir ↓Lopinavir	An increased rate of adverse events has been observed. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Saquinavir ^a	LEXIVA: ↓Amprenavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.

	<p>Effect on saquinavir is not well established.</p> <p>LEXIVA/ritonavir: Interaction has not been evaluated.</p>	
<p>HIV integrase inhibitor: Raltegravir^a</p>	<p>LEXIVA: ↓Amprenavir ↓Raltegravir</p> <p>LEXIVA/ritonavir: ↓Amprenavir ↓Raltegravir</p>	<p>Appropriate doses of the combination with respect to safety and efficacy have not been established [see <i>Clinical Pharmacology (12.3)</i>].</p>
Other Agents		
<p>Antiarrhythmics: Amiodarone, bepridil, lidocaine (systemic), and quinidine</p>	<p>↑Antiarrhythmics</p>	<p>Use with caution. Increased exposure may be associated with life-threatening reactions such as cardiac arrhythmias. Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics.</p>
<p>Anticoagulant: Warfarin</p>		<p>Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.</p>
<p>Anticonvulsants: Carbamazepine, phenobarbital, phenytoin</p> <p>Phenytoin^a</p>	<p>LEXIVA: ↓Amprenavir</p> <p>LEXIVA/ritonavir: ↑Amprenavir ↓Phenytoin</p>	<p>Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.</p> <p>Plasma phenytoin concentrations should be monitored and phenytoin dose should be increased as appropriate. No change in LEXIVA/ritonavir dose is recommended.</p>
<p>Antidepressant: Paroxetine, trazodone</p>	<p>↓Paroxetine</p>	<p>Coadministration of paroxetine with LEXIVA/ritonavir significantly decreased plasma levels of paroxetine. Any paroxetine dose adjustment should be guided by clinical effect (tolerability and</p>

	↑Trazodone	<p>efficacy).</p> <p>Concomitant use of trazodone and LEXIVA with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as LEXIVA, the combination should be used with caution and a lower dose of trazodone should be considered.</p>
<p>Antifungals: Ketoconazole^a, itraconazole</p>	<p>↑Ketoconazole ↑Itraconazole</p>	<p>Increase monitoring for adverse events.</p> <p>LEXIVA: Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.</p> <p>LEXIVA/ritonavir: High doses of ketoconazole or itraconazole (greater than 200 mg/day) are not recommended.</p>
<p>Anti-gout: Colchicine</p>	↑Colchicine	<p>Patients with renal or hepatic impairment should not be given colchicine with LEXIVA/ritonavir.</p> <p>LEXIVA/ritonavir and coadministration of colchicine:</p> <p>Treatment of gout flares: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.</p>

		<p>If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p>Treatment of familial Mediterranean fever (FMF): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p> <p>LEXIVA and coadministration of colchicine:</p> <p>Treatment of gout flares: 1.2 mg (2 tablets) x 1 dose. Dose to be 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>

Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑Benzodiazepines	Clinical significance is unknown. A decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑Calcium channel blockers	Use with caution. Clinical monitoring of 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	↑Salmeterol	Concurrent administration of salmeterol with LEXIVA is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
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, vardenafil	↑Sildenafil ↑Tadalafil ↑Vardenafil	<p>May result in an increase in PDE5 inhibitor-associated adverse events, 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.</p>

		<p>Tadalafil: no more than 10 mg every 72 hours.</p> <p>Vardenafil: no more than 2.5 mg every 24 hours.</p> <p>LEXIVA/ritonavir:</p> <p>Sildenafil: 25 mg every 48 hours.</p> <p>Tadalafil: no more than 10 mg every 72 hours.</p> <p>Vardenafil: no more than 2.5 mg every 72 hours.</p> <p>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>

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

294 **8 USE IN SPECIFIC POPULATIONS**

295 **8.1 Pregnancy**

296 Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed
297 from day 6 to day 17 of gestation) and rabbits (dosed from day 7 to day 20 of gestation).

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

308 The mating and fertility of the F₁ generation born to female rats given fosamprenavir was
309 not different from control animals; however, fosamprenavir did cause a reduction in both pup

310 survival and body weights. Surviving F₁ female rats showed an increased time to successful
311 mating, an increased length of gestation, a reduced number of uterine implantation sites per litter,
312 and reduced gestational body weights compared with control animals. Systemic exposure
313 (AUC_{0-24 hr}) to amprenavir in the F₀ pregnant rats was approximately 2 times higher than
314 exposures in humans following administration of the MRHD of fosamprenavir alone or
315 approximately the same as those seen in humans following administration of the MRHD of
316 fosamprenavir in combination with ritonavir.

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

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

322 **8.3 Nursing Mothers**

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

329 **8.4 Pediatric Use**

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

337 Treatment with LEXIVA is not recommended in protease inhibitor-experienced pediatric
338 patients less than 6 months of age. The pharmacokinetics, safety, tolerability, and efficacy of
339 LEXIVA in pediatric patients less than 4 weeks of age have not been established [*see Clinical*
340 *Pharmacology (12.3)*]. Available pharmacokinetic and clinical data do not support once-daily
341 dosing of LEXIVA alone or in combination with ritonavir for any pediatrics or twice-daily
342 dosing without ritonavir in pediatric patients less than 2 years of age [*see Clinical Pharmacology*
343 *(12.3) and Clinical Studies (14.3)*]. See *Dosage and Administration (2.2)* for dosing
344 recommendations for pediatric patients.

345 **8.5 Geriatric Use**

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

350 **8.6 Hepatic Impairment**

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

356 There are no data to support dosing recommendations for pediatric subjects with hepatic
357 impairment.

358 **10 OVERDOSAGE**

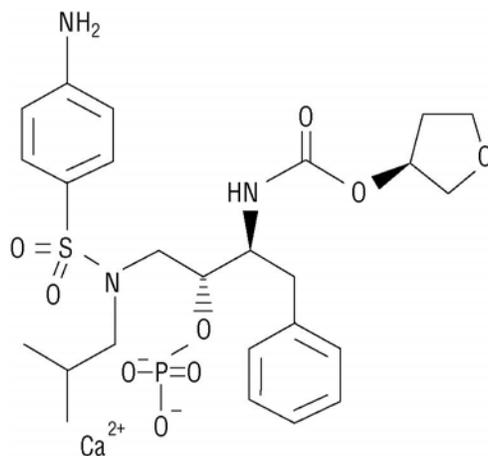
359 In a healthy volunteer repeat-dose pharmacokinetic study evaluating high-dose
360 combinations of LEXIVA plus ritonavir, an increased frequency of Grade 2/3 ALT elevations
361 (greater than 2.5 x ULN) was observed with LEXIVA 1,400 mg twice daily plus ritonavir
362 200 mg twice daily (4 of 25 subjects). Concurrent Grade 1/2 elevations in AST (greater than
363 1.25 x ULN) were noted in 3 of these 4 subjects. These transaminase elevations resolved
364 following discontinuation of dosing.

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

368 **11 DESCRIPTION**

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

375



376
377

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

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

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

392 12 CLINICAL PHARMACOLOGY

393 12.1 Mechanism of Action

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

395 12.3 Pharmacokinetics

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

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

402

403 **Table 8. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
404 **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)

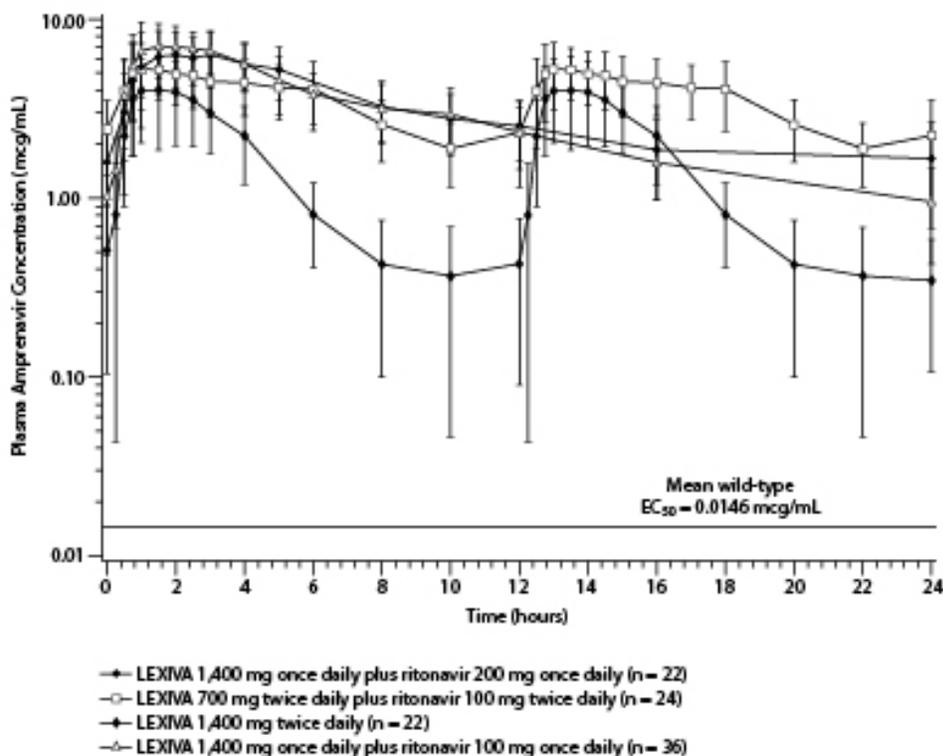
405 ^a Data shown are median (range).

406

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

409

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



413

414

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

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

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

427 Administration of a single 1,400 mg dose of LEXIVA Oral Suspension in the fed state
428 (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate)

429 compared with the fasted state was associated with a 46% reduction in C_{\max} , a 0.72-hour delay in
430 T_{\max} , and a 28% reduction in amprenavir $AUC_{0-\infty}$.

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

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

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

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

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

461 The pharmacokinetics of amprenavir have been studied after administration of
462 amprenavir given as AGENERASE[®] Capsules to adult subjects with hepatic impairment.
463 Following administration of a single 600 mg oral dose, the AUC of amprenavir was increased by
464 approximately 2.5-fold in subjects with moderate cirrhosis and by approximately 4.5-fold in
465 subjects with severe cirrhosis compared with healthy volunteers [*see Dosage and Administration*
466 *(2.3)*].

467 **Renal Impairment:** The impact of renal impairment on amprenavir elimination in
468 adults has not been studied. The renal elimination of unchanged amprenavir represents

469 approximately 1% of the administered dose; therefore, renal impairment is not expected to
470 significantly impact the elimination of amprenavir.

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

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

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

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

494

495 **Table 9. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic**
496 **Parameters by Weight in Pediatric and Adolescent Subjects Aged at Least 4 Weeks to 18**
497 **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)

498 ^a Recommend dose for pediatric subjects weighing 11 kg to less than 15 kg is based on
499 population pharmacokinetic analysis.
500

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

504 **Geriatric Patients:** The pharmacokinetics of amprenavir after administration of
505 LEXIVA to patients older than 65 years have not been studied [see *Use in Specific Populations*
506 (8.5)].

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

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

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

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

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

526

527 **Table 10. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**528 **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)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	↔ ^c	↔ ^c	↔ ^c
Nevirapine 200 mg b.i.d. for 2 weeks ^f	1,400 mg b.i.d. for 2 weeks	17	↓25 (↓37 to ↓10)	↓33 (↓45 to ↓20)	↓35 (↓50 to ↓15)
Nevirapine 200 mg b.i.d. for 2 weeks ^f	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↔	↓11 (↓23 to ↑3)	↓19 (↓32 to ↓4)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	13	↔	↑20 (↑8 to ↑34)	↑19 (↑6 to ↑33)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg b.i.d. for 14 days (fasted)	14	↓27 (↓46 to ↔)	↓36 (↓53 to ↓13)	↓43 ^g (↓59 to ↓21)
	1,400 mg b.i.d. for 14 days ^h	14	↓15 (↓27 to ↓1)	↓17 (↓27 to ↓6)	↓32 ^g (↓53 to ↓1)
	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days (fasted)	14	↓14 (↓39 to ↑20)	↓17 (↓38 to ↑12)	↓20 ^g (↓45 to ↑17)

	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days ^h	12	↓25 (↓42 to ↓2)	↓25 (↓44 to ↔)	↓33 ^g (↓52 to ↓7)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days (fasted)	13	↓18 (↓34 to ↔)	↓24 (↓41 to ↔)	↓50 ^g (↓64 to ↓31)
	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days ^h	14	↑27 (↓1 to ↑62)	↑13 (↓7 to ↑38)	↓17 ^g (↓45 to ↑26)
Ranitidine 300 mg single dose (administered 1 hour before fosamprenavir)	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	↔ (↓19 to ↑21)
Rifabutin 150 mg q.o.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↑36 ^c (↑18 to ↑55)	↑35 ^c (↑17 to ↑56)	↑17 ^c (↓1 to ↑39)
Tenofovir 300 mg q.d. for 4 to 48 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 to 48 weeks	45	NA	NA	↔ ⁱ
Tenofovir 300 mg q.d. for 4 to 48 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 4 to 48 weeks	60	NA	NA	↔ ⁱ

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

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

532 ^c Compared with historical control.

533 ^d Subjects were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period
534 with both ketoconazole and LEXIVA/ritonavir.

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

536 ^f Subjects were receiving nevirapine for at least 12 weeks prior to study.

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

538 ^h Doses of LEXIVA and raltegravir were given with food on pharmacokinetic sampling days
539 and without regard to food all other days.

540 ⁱ Compared with parallel control group.

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

543

544 **Table 11. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After**
 545 **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

546 ^a Compared with parallel control group.

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

548 ^c Compared with historical data.

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

551

552 **Table 12. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
553 **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 (↑10 to ↑56)	↑169 (↑108 to ↑248)	ND
Lopinavir/ritonavir ^e 533 mg/133 mg b.i.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	18	↔ ^f	↔ ^f	↔ ^f
Lopinavir/ritonavir ^e 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↑30 (↓15 to ↑47)	↑37 (↓20 to ↑55)	↑52 (↓28 to ↑82)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	R-Methadone (active)		
			↓21 ^g (↓30 to ↓12)	↓18 ^g (↓27 to ↓8)	↓11 ^g (↓21 to ↑1)
			S-Methadone (inactive)		
			↓43 ^g (↓49 to ↓37)	↓43 ^g (↓50 to ↓36)	↓41 ^g (↓49 to ↓31)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	1,400 mg b.i.d. for 2 weeks	17	↑25 (↑14 to ↑37)	↑29 (↑19 to ↑40)	↑34 (↑20 to ↑49)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↑13 (↑3 to ↑24)	↑14 (↑5 to ↑24)	↑22 (↑9 to ↑35)
Norethindrone ^c 0.5 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓38 (↓32 to ↓44)	↓34 (↓30 to ↓37)	↓26 (↓20 to ↓32)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	14	↓20 (↓12 to ↓27)	↓22 (↓17 to ↓27)	↓29 (↓23 to ↓34)

Rifabutin 150 mg every other day for 2 weeks ⁱ (25-O-desacetylriofabutin metabolite) Rifabutin + 25-O- desacetylriofabutin metabolite	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↓14 (↓28 to ↑4) ↑579 (↑479 to ↑698) NA	↔ ↑1,120 (↑965 to ↑1,300) ↑64 (↑46 to ↑84)	↑28 (↑12 to ↑46) ↑2,510 (↑1,910 to ↑3,300) NA
Rosuvastatin 10 mg single dose	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 7 days		↑45	↑8	NA

- 554 ^a Concomitant medication is also shown in this column where appropriate.
- 555 ^b Comparison arm of atazanavir 300 mg q.d. plus ritonavir 100 mg q.d. for 10 days.
- 556 ^c Administered as a combination oral contraceptive tablet: ethinyl estradiol 0.035 mg/
557 norethindrone 0.5 mg.
- 558 ^d Subjects were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with
559 both ketoconazole and LEXIVA/ritonavir.
- 560 ^e Data represent lopinavir concentrations.
- 561 ^f Compared with lopinavir 400 mg/ritonavir 100 mg b.i.d. for 2 weeks.
- 562 ^g Dose normalized to methadone 100 mg. The unbound concentration of the active moiety,
563 R-methadone, was unchanged.
- 564 ^h Subjects were receiving nevirapine for at least 12 weeks prior to study.
- 565 ⁱ Comparison arm of rifabutin 300 mg q.d. for 2 weeks. AUC is AUC_(0-48 hr).
- 566 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ less than 10%); ND = Interaction cannot be
567 determined as C_{min} was below the lower limit of quantitation.
- 568

569 **Table 13. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in**
570 **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 44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16	R-Methadone (active)		
			↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
			S-Methadone (inactive)		
			↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
Nelfinavir 750 mg t.i.d. for 2 weeks (fed)	750 mg or 800 mg t.i.d. for 2 weeks (fed)	6	↑12 ^a	↑15 ^a	↑14 ^a
Norethindrone 1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↑18 (↑1 to ↑38)	↑45 (↑13 to ↑88)
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↔	↔	ND
Saquinavir 800 mg t.i.d. for 2 weeks (fed)	750 mg or 800 mg t.i.d. for 2 weeks (fed)	7	↑21 ^a	↓19 ^a	↓48 ^a
Zidovudine 300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA

571 ^a Compared with historical data.

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

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

576

577 12.4 Microbiology

578 Mechanism of Action: Fosamprenavir is a prodrug that is rapidly hydrolyzed to
579 amprenavir by cellular phosphatases in the gut epithelium as it is absorbed. Amprenavir is an
580 inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby

581 prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the
582 formation of immature non-infectious viral particles.

583 **Antiviral Activity:** Fosamprenavir has little or no antiviral activity in cell culture. The
584 antiviral activity of amprenavir was evaluated against HIV-1 IIB in both acutely and chronically
585 infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes
586 in cell culture. The 50% effective concentration (EC₅₀) of amprenavir ranged from 0.012 to
587 0.08 microM in acutely infected cells and was 0.41 microM in chronically infected cells
588 (1 microM = 0.50 mcg per mL). The median EC₅₀ value of amprenavir against HIV-1 isolates
589 from clades A to G was 0.00095 microM in peripheral blood mononuclear cells (PBMCs).
590 Similarly, the EC₅₀ values for amprenavir against monocytes/macrophage tropic HIV-1 isolates
591 (clade B) ranged from 0.003 to 0.075 microM in monocyte/macrophage cultures. The EC₅₀
592 values of amprenavir against HIV-2 isolates grown in PBMCs were higher than those for HIV-1
593 isolates, and ranged from 0.003 to 0.11 microM. Amprenavir exhibited synergistic anti-HIV-1
594 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir,
595 didanosine, lamivudine, stavudine, tenofovir, and zidovudine; the non-nucleoside reverse
596 transcriptase inhibitors (NNRTIs) delavirdine and efavirenz; and the protease inhibitors
597 atazanavir and saquinavir. Amprenavir exhibited additive anti-HIV-1 activity in combination
598 with the NNRTI nevirapine, the protease inhibitors indinavir, lopinavir, nelfinavir, and ritonavir;
599 and the fusion inhibitor enfuvirtide. These drug combinations have not been adequately studied
600 in humans.

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

620 using an ultrasensitive assay, these resistant substitutions were traced back to Week 84
 621 (76 weeks prior to clinical virologic failure).

622 **Cross-Resistance:** Varying degrees of cross-resistance among HIV-1 protease
 623 inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1
 624 RNA level less than 400 copies per mL) and protease inhibitor-resistance substitutions detected
 625 in baseline HIV-1 isolates from protease inhibitor-experienced subjects receiving
 626 LEXIVA/ritonavir twice daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in Trial
 627 APV30003 is shown in Table 14. The majority of subjects had previously received either one
 628 (47%) or 2 protease inhibitors (36%), most commonly nelfinavir (57%) and indinavir (53%). Out
 629 of 102 subjects with baseline phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (n = 55)
 630 had resistance to at least one protease inhibitor, with 98% (n = 54) of those having resistance to
 631 nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60%
 632 (n = 58) had resistance to at least one protease inhibitor, with 97% (n = 56) of those having
 633 resistance to nelfinavir.

634

635 **Table 14. Responders at Trial Week 48 by Presence of Baseline Protease Inhibitor**
 636 **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%

637 ^a Results should be interpreted with caution because the subgroups were small.

638 ^b Most subjects had greater than 1 protease inhibitor resistance-associated substitution
 639 at baseline.

640

641 The virologic response based upon baseline phenotype was assessed. Baseline isolates
 642 from protease inhibitor-experienced subjects responding to LEXIVA/ritonavir twice daily had a
 643 median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of
 644 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a
 645 median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient

646 population, these data do not constitute definitive clinical susceptibility break points. Additional
647 data are needed to determine clinically relevant break points for LEXIVA.

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

655 **13 NONCLINICAL TOXICOLOGY**

656 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

657 In long-term carcinogenicity studies, fosamprenavir was administered orally for up to
658 104 weeks at doses of 250, 400, or 600 mg per kg per day in mice and at doses of 300, 825, or
659 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
660 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to
661 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of
662 fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were
663 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir
664 plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and
665 hepatocellular carcinomas at all doses in male mice and at 600 mg per kg per day in female mice,
666 and in hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and
667 at 835 mg per kg per day and 2,250 mg per kg per day in female rats. The relevance of the
668 hepatocellular findings in the rodents for humans is uncertain. Repeat dose studies with
669 fosamprenavir in rats produced effects consistent with enzyme induction, which predisposes rats,
670 but not humans, to thyroid neoplasms. In addition, in rats only there was an increase in
671 interstitial cell hyperplasia at 825 mg per kg per day and 2,250 mg per kg per day, and an
672 increase in uterine endometrial adenocarcinoma at 2,250 mg per kg per day. The incidence of
673 endometrial findings was slightly increased over concurrent controls, but was within background
674 range for female rats. The relevance of the uterine endometrial adenocarcinoma findings in rats
675 for humans is uncertain.

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

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

685 impair mating or fertility of male or female rats and did not affect the development and
686 maturation of sperm from treated rats.

687 **14 CLINICAL STUDIES**

688 **14.1 Therapy-Naive Adult Trials**

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

693 The mean age of the subjects in this study was 37 years (range: 17 to 70 years); 69% of
694 the subjects were male, 20% were CDC Class C (AIDS), 24% were Caucasian, 32% were black,
695 and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells per mm³ (range:
696 2 to 1,136 cells per mm³; 18% of subjects had a CD4+ cell count of less than 50 cells per mm³
697 and 30% were in the range of 50 to less than 200 cells per mm³). Baseline median HIV-1 RNA
698 was 4.83 log₁₀ copies per mL (range: 1.69 to 7.41 log₁₀ copies per mL; 45% of subjects had
699 greater than 100,000 copies per mL).

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

701

702 **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%

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

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

708

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

710

711 **Table 16. Proportions of Responders Through Week 48 by Screening Viral Load**
 712 **(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

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

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

721 The mean age of the subjects in this study was 37 years (range: 18 to 69 years); 73% of
 722 the subjects were male, 22% were CDC Class C, 53% were Caucasian, 36% were black, and 8%
 723 were Hispanic. At baseline, the median CD4+ cell count was 170 cells per mm³ (range: 1 to
 724 1,055 cells per mm³; 20% of subjects had a CD4+ cell count of less than 50 cells per mm³ and
 725 35% were in the range of 50 to less than 200 cells per mm³). Baseline median HIV-1 RNA was
 726 4.81 log₁₀ copies per mL (range: 2.65 to 7.29 log₁₀ copies per mL; 43% of subjects had greater
 727 than 100,000 copies per mL).

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

729

730 **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%

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

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

736

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

738

739 **Table 18. Proportions of Responders Through Week 48 by Screening Viral Load**
 740 **(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

741

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

745 **14.2 Protease Inhibitor-Experienced Adult Trials**

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

751 The mean age of the subjects in this study was 42 years (range: 24 to 72 years); 85%
 752 were male, 33% were CDC Class C, 67% were Caucasian, 24% were black, and 9% were
 753 Hispanic. The median CD4+ cell count at baseline was 263 cells per mm³ (range: 2 to 1,171 cells

754 per mm³). Baseline median plasma HIV-1 RNA level was 4.14 log₁₀ copies per mL (range: 1.69
755 to 6.41 log₁₀ copies per mL).

756 The median durations of prior exposure to NRTIs were 257 weeks for subjects receiving
757 LEXIVA/ritonavir twice daily (79% had greater than or equal to 3 prior NRTIs) and 210 weeks
758 for subjects receiving lopinavir/ritonavir (64% had greater than or equal to 3 prior NRTIs). The
759 median durations of prior exposure to protease inhibitors were 149 weeks for subjects receiving
760 LEXIVA/ritonavir twice daily (49% received greater than or equal to 2 prior protease inhibitors)
761 and 130 weeks for subjects receiving lopinavir/ritonavir (40% received greater than or equal to
762 2 prior protease inhibitors).

763 The time-averaged changes in plasma HIV-1 RNA from baseline (AAUCMB) at
764 48 weeks (the endpoint on which the study was powered) were -1.4 log₁₀ copies per mL for
765 twice-daily LEXIVA/ritonavir and -1.67 log₁₀ copies per mL for the lopinavir/ritonavir group.

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

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

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

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

780 Once-daily administration of LEXIVA plus ritonavir is not recommended for protease
781 inhibitor-experienced patients. Through Week 48, 50% and 37% of subjects receiving LEXIVA
782 1,400 mg plus ritonavir 200 mg once daily had plasma HIV-1 RNA less than 400 copies per mL
783 and less than 50 copies per mL, respectively.

784 **14.3 Pediatric Trials**

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

793 APV29005: LEXIVA: Twenty (18 therapy-naive and 2 therapy-experienced) pediatric
794 subjects received LEXIVA Oral Suspension without ritonavir twice daily. At Week 24, 65%
795 (13/20) achieved HIV-1 RNA less than 400 copies per mL, and the median increase from
796 baseline in CD4+ cell count was 350 cells per mm³.

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

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

808 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

812 Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C
813 (59° to 86°F) (see USP Controlled Room Temperature). Keep container tightly closed.

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

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

818 This product does not require reconstitution.

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

821 **17 PATIENT COUNSELING INFORMATION**

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

823 **17.1 Drug Interactions**

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

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

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

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

835 **17.2 Sulfa Allergy**

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

838 **17.3 Redistribution/Accumulation of Body Fat**

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

842 **17.4 Information About Therapy With LEXIVA**

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

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

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

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

864 **17.5 Oral Suspension**

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

867

868 LEXIVA and AGENERASE are registered trademarks of ViiV Healthcare.

869

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

873
874

875 Manufactured for:



ViiV Healthcare
Research Triangle Park, NC 27709



Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

876
877

by:



GlaxoSmithKline

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880 Research Triangle Park, NC 27709
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LXV:PI

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

888
889

PATIENT INFORMATION

890
891

LEXIVA[®] (lex-EE-vah)
(fosamprenavir calcium)

892
893

Tablets

and

894
895

Oral Suspension

896 **Important: LEXIVA can interact with other medicines and cause serious**
897 **side effects. It is important to know the medicines that should not be taken**
898 **with LEXIVA. See the section “Who should not take LEXIVA?”**
899

900 Read this Patient Information before you start taking LEXIVA and each time you get
901 a refill. There may be new information. This information does not take the place of
902 talking with your healthcare provider about your medical condition or treatment.
903

904 **What is LEXIVA?**

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

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

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

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

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

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

921 Avoid doing things that can spread HIV infection to others.

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

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

930

931 **Who should not take LEXIVA?**

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

- 933 • alfuzosin (UROXATRAL®)
- 934 • flecainide (TAMBOCOR™)
- 935 • propafenone (RYTHMOL SR®)
- 936 • rifampin (RIFADIN®, RIFAMATE®, RIFATER®, RIMACTANE®)
- 937 • ergot including:
- 938 • dihydroergotamine mesylate (D.H.E. 45®, MIGRANAL®)
- 939 • ergotamine tartrate (CAFERGOT®, MIGERGOT®, ERGOMAR®, MEDIHALER
940 ERGOTAMINE®)

- 941 • methylergonovine (METHERGINE®)
- 942 • St. John's wort (*Hypericum perforatum*)
- 943 • lovastatin (ADVICOR®, ALTOPREV®, MEVACOR®)
- 944 • simvastatin (ZOCOR®, VYTORIN®, SIMCOR®)
- 945 • pimozide (ORAP®)
- 946 • delavirdine mesylate (RESCRIPTOR®)
- 947 • sildenafil (REVATIO®), for treatment of pulmonary arterial hypertension
- 948 • triazolam (HALCION®)

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

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

954

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

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

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

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

- 969 • **Do not breastfeed.** We do not know if LEXIVA can be passed to your baby in
970 your breast milk and whether it could harm your baby. Also, mothers with HIV
971 should not breastfeed because HIV can be passed to the baby in the breast milk.

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

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

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

982 Know all the medicines that you take. Keep a list of them with you to show
983 healthcare providers and pharmacists when you get a new medicine.
984

985 **How should I take LEXIVA?**

- 986 • **Stay under the care of a healthcare provider while taking LEXIVA.**
- 987 • Take LEXIVA exactly as prescribed by your healthcare provider.
- 988 • Do not change your dose or stop taking LEXIVA without talking with your
989 healthcare provider.
- 990 • If your child is taking LEXIVA, your child's healthcare provider will decide the
991 right dose based on your child's weight.
- 992 • You can take LEXIVA Tablets with or without food.
- 993 • **Adults should take LEXIVA Oral Suspension without food.**
- 994 • **Children should take LEXIVA Oral Suspension with food.** If your child
995 vomits within 30 minutes after taking a dose of LEXIVA, the dose should be
996 repeated.
- 997 • Shake LEXIVA Oral Suspension well before each use.
- 998 • If you miss a dose of LEXIVA, take the next dose as soon as possible and then
999 take your next dose at the regular time. Do not double the next dose. If you take
1000 too much LEXIVA, call your healthcare provider or go to the nearest hospital
1001 emergency room right away.
1002

1003 **What are the possible side effects of LEXIVA?**

1004 **LEXIVA may cause serious side effects including:**

- 1005 • **Severe skin rash.** LEXIVA may cause severe or life-threatening skin reactions
1006 or rash.

1007 **If you get a rash with any of the following symptoms, stop taking**
1008 **LEXIVA and call your healthcare provider or get medical help right**
1009 **away:**

- 1010 • hives or sores in your mouth, or your skin blisters and peels
- 1011 • trouble swallowing or breathing
- 1012 • swelling of your face, eyes, lips, tongue, or throat

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

1044 **The most common side effects of LEXIVA in adults include:**

- 1045 • nausea
- 1046 • vomiting
- 1047 • diarrhea
- 1048 • headache

1049 Vomiting is the most common side effect in children when taking LEXIVA.

1050 Tell your healthcare provider about any side effect that bothers you or that does
1051 not go away.

1052 These are not all the possible side effects of LEXIVA. For more information, ask
1053 your healthcare provider or pharmacist.
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.

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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
1100 Manufactured for:



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Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

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