

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

Warnings and Precautions, Risk of Serious Adverse Reactions Due to Drug Interactions (5.1) 03/2015

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-naïve 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(3)
- 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

- The concomitant use of LEXIVA with ritonavir and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.3)
- 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, and headache. (6.1)
- Vomiting and neutropenia were more frequent in pediatrics than in adults. (6.1)

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

DRUG INTERACTIONS

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Adults
- 2.2 Pediatric Patients (Aged at Least 4 Weeks to 18 Years)
- 2.3 Patients with Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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

6 ADVERSE REACTIONS

- 6.1 Clinical Trials
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Cytochrome P450 Inhibitors and Inducers

7.2 Drugs that Should Not Be Coadministered with LEXIVA

7.3 Established and Other Potentially Significant Drug Interactions

8 USE IN SPECIFIC POPULATIONS

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

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Therapy-naïve Adult Trials
- 14.2 Protease Inhibitor-experienced Adult Trials
- 14.3 Pediatric Trials

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

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

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

- 7 • The protease inhibitor-experienced patient trial was not large enough to reach a definitive
8 conclusion that LEXIVA plus ritonavir and lopinavir plus ritonavir are clinically equivalent
9 [see *Clinical Studies (14.2)*].
- 10 • Once-daily administration of LEXIVA plus ritonavir is not recommended for adult protease
11 inhibitor-experienced patients or any pediatric patients [see *Dosage and Administration (2.1,*
12 *2.2), Clinical Studies (14.2, 14.3)*].
- 13 • Dosing of LEXIVA plus ritonavir is not recommended for protease inhibitor-experienced
14 pediatric patients younger than 6 months [see *Clinical Pharmacology (12.3)*].

15 2 DOSAGE AND ADMINISTRATION

16 LEXIVA tablets may be taken with or without food.

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

20 Higher-than-approved dose combinations of LEXIVA plus ritonavir are not recommended due to
21 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 should be
38 calculated based on body weight (kg) and should not exceed the recommended adult dose
39 (Table 1).

40 **Table 1. Twice-daily Dosage Regimens by Weight for Protease Inhibitor-naive**
41 **Pediatric Patients (Greater than or Equal to 4 Weeks of Age) and for Protease**
42 **Inhibitor-experienced Pediatric Patients (Greater than or Equal to 6 Months of**
43 **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

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

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

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

50 For pediatric patients, pharmacokinetic and clinical data:

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

57 **Other Dosing Considerations**

- 58 • When administered without ritonavir, the adult regimen of LEXIVA tablets 1,400 mg twice
59 daily may be used for pediatric patients weighing at least 47 kg.

- 60 • When administered in combination with ritonavir, LEXIVA tablets may be used for pediatric
61 patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients
62 weighing at least 33 kg.

63 **2.3 Patients with Hepatic Impairment**

64 *See Clinical Pharmacology (12.3).*

65 Mild Hepatic Impairment (Child-Pugh Score Ranging from 5 to 6)

66 LEXIVA should be used with caution at a reduced dosage of 700 mg twice daily without
67 ritonavir (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive
68 or protease inhibitor-experienced).

69 Moderate Hepatic Impairment (Child-Pugh Score Ranging from 7 to 9)

70 LEXIVA should be used with caution at a reduced dosage of 700 mg twice daily without
71 ritonavir (therapy-naive), or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive
72 or protease inhibitor-experienced).

73 Severe Hepatic Impairment (Child-Pugh Score Ranging from 10 to 15)

74 LEXIVA should be used with caution at a reduced dosage of 350 mg twice daily without
75 ritonavir (therapy-naive) or 300 mg twice daily plus ritonavir 100 mg once daily (therapy-naive
76 or protease inhibitor-experienced).

77 There are no data to support dosing recommendations for pediatric patients with hepatic
78 impairment.

79 **3 DOSAGE FORMS AND STRENGTHS**

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

82 LEXIVA oral suspension, 50 mg per mL, is a white to off-white suspension that has a
83 characteristic grape-bubblegum-peppermint flavor.

84 **4 CONTRAINDICATIONS**

85 LEXIVA is contraindicated:

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

91 **Table 2. Drugs Contraindicated with LEXIVA (Information in the table applies to**
 92 **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.

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

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

97 **5 WARNINGS AND PRECAUTIONS**

98 **5.1 Risk of Serious Adverse Reactions Due to Drug Interactions**

99 Initiation of LEXIVA/ritonavir, a CYP3A inhibitor, in patients receiving medications
100 metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already
101 receiving LEXIVA/ritonavir, may increase plasma concentrations of medications metabolized by
102 CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease
103 concentrations of LEXIVA/ritonavir, respectively. These interactions may lead to:

- 104 • Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal
105 events from greater exposures of concomitant medications.
106 • Clinically significant adverse reactions from greater exposures of LEXIVA/ritonavir.
107 • Loss of therapeutic effect of LEXIVA/ritonavir and possible development of resistance.

108 See Table 7 for steps to prevent or manage these possible and known significant drug
109 interactions, including dosing recommendations [*see Drug Interactions (7)*]. Consider the
110 potential for drug interactions prior to and during LEXIVA/ritonavir therapy; review
111 concomitant medications during LEXIVA/ritonavir therapy; and monitor for the adverse
112 reactions associated with the concomitant medications [*see Contraindications (4), Drug*
113 *Interactions (7)*].

114 **5.2 Skin Reactions**

115 Severe and life-threatening skin reactions, including 1 case of Stevens-Johnson syndrome among
116 700 subjects treated with LEXIVA in clinical trials. Treatment with LEXIVA should be
117 discontinued for severe or life-threatening rashes and for moderate rashes accompanied by
118 systemic symptoms [*see Adverse Reactions (6)*].

119 **5.3 Sulfa Allergy**

120 LEXIVA should be used with caution in patients with a known sulfonamide allergy.
121 Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs
122 in the sulfonamide class and fosamprenavir is unknown. In a clinical trial of LEXIVA used as
123 the sole protease inhibitor, rash occurred in 2 of 10 subjects (20%) with a history of sulfonamide
124 allergy compared with 42 of 126 subjects (33%) with no history of sulfonamide allergy. In
125 2 clinical trials of LEXIVA plus low-dose ritonavir, rash occurred in 8 of 50 subjects (16%) with
126 a history of sulfonamide allergy compared with 50 of 412 subjects (12%) with no history of
127 sulfonamide allergy.

128 **5.4 Hepatic Toxicity**

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

135 **5.5 Diabetes/Hyperglycemia**

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

144 **5.6 Immune Reconstitution Syndrome**

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

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

154 **5.7 Fat Redistribution**

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

160 **5.8 Lipid Elevations**

161 Treatment with LEXIVA plus ritonavir has resulted in increases in the concentration of
162 triglycerides and cholesterol [*see Adverse Reactions (6)*]. Triglyceride and cholesterol testing

163 should be performed prior to initiating therapy with LEXIVA and at periodic intervals during
164 therapy. Lipid disorders should be managed as clinically appropriate [see *Drug Interactions (7)*].

165 **5.9 Hemolytic Anemia**

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

167 **5.10 Patients with Hemophilia**

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

172 **5.11 Nephrolithiasis**

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

177 **5.12 Resistance/Cross-resistance**

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

182 **6 ADVERSE REACTIONS**

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

191 **6.1 Clinical Trials**

192 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
193 observed in the clinical trials of a drug cannot be directly compared with rates in the clinical
194 trials of another drug and may not reflect the rates observed in clinical practice.

195 Adult Trials

196 The data for the 3 active-controlled clinical trials described below reflect exposure of
 197 700 HIV-1–infected subjects to LEXIVA tablets, including 599 subjects exposed to LEXIVA for
 198 greater than 24 weeks, and 409 subjects exposed for greater than 48 weeks. The population age
 199 ranged from 17 to 72 years. Of these subjects, 26% were female, 51% white, 31% black, 16%
 200 American Hispanic, and 70% were antiretroviral-naive. Sixty-one percent received LEXIVA
 201 1,400 mg once daily plus ritonavir 200 mg once daily; 24% received LEXIVA 1,400 mg twice
 202 daily; and 15% received LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily.

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

206 **Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater than or**
 207 **Equal to 2% of Antiretroviral-naive Adult Subjects**

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

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

209 **Table 4. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater than or**
 210 **Equal to 2% of Protease Inhibitor-experienced Adult Subjects (Trial 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%

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

212 Skin rash (without regard to causality) occurred in approximately 19% of subjects treated with
 213 LEXIVA in the pivotal efficacy trials. Rashes were usually maculopapular and of mild or
 214 moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of
 215 LEXIVA and had a median duration of 13 days. Skin rash led to discontinuation of LEXIVA in
 216 less than 1% of subjects. In some subjects with mild or moderate rash, dosing with LEXIVA was
 217 often continued without interruption; if interrupted, reintroduction of LEXIVA generally did not
 218 result in rash recurrence.

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

221 **Table 5. Grade 3/4 Laboratory Abnormalities Reported in Greater than or Equal to 2% of**
 222 **Antiretroviral-naive Adult Subjects in Trials 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%

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

224 ^b Fasting specimens.

225 ULN = Upper limit of normal.

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

228 **Table 6. Grade 3/4 Laboratory Abnormalities Reported in Greater than or Equal to 2% of**
 229 **Protease Inhibitor-experienced Adult Subjects in Trial 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

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

231 ^b Fasting specimens.

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

233 ULN = Upper limit of normal.

234 Pediatric Trials

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

238 subjects compared with adults. Other adverse events occurred with similar frequency in pediatric
239 subjects compared with adults.

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

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

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

253 **6.2 Postmarketing Experience**

254 In addition to adverse reactions reported from clinical trials, the following reactions have been
255 identified during post-approval use of LEXIVA. Because they are reported voluntarily from a
256 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

260 Myocardial infarction.

261 Metabolism and Nutrition Disorders

262 Hypercholesterolemia.

263 Nervous System Disorders

264 Oral paresthesia.

265 Skin and Subcutaneous Tissue Disorders

266 Angioedema.

267 Urogenital

268 Nephrolithiasis.

269 **7 DRUG INTERACTIONS**

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

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

273 **7.1 Cytochrome P450 Inhibitors and Inducers**

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

277 Amprenavir is metabolized by CYP3A4. Coadministration of LEXIVA and drugs that induce
278 CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its therapeutic
279 effect. Coadministration of LEXIVA and drugs that inhibit CYP3A4 may increase amprenavir
280 concentrations and increase the incidence of adverse effects.

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

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

289 **7.2 Drugs that Should Not Be Coadministered with LEXIVA**

290 *See Contraindications (4)*.

291 **7.3 Established and Other Potentially Significant Drug Interactions**

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

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

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

HCV protease inhibitor: Telaprevir ^a	LEXIVA/ritonavir: ↓Amprenavir ↓Telaprevir	Coadministration of LEXIVA/ritonavir and telaprevir is not recommended.
HCV protease inhibitor: Boceprevir	LEXIVA/ritonavir: ↓Amprenavir (predicted) ↓Boceprevir (predicted)	Coadministration of LEXIVA/ritonavir and boceprevir is not recommended. A pharmacokinetic interaction has been reported between boceprevir and some HIV protease inhibitors in combination with ritonavir, leading to decreased HIV protease inhibitor concentrations and, in some cases, decreased boceprevir concentrations.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz ^a	LEXIVA: ↓Amprenavir LEXIVA/ritonavir: ↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with LEXIVA/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with LEXIVA plus ritonavir twice daily.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine ^a	LEXIVA: ↓Amprenavir ↑Nevirapine LEXIVA/ritonavir: ↓Amprenavir ↑Nevirapine	Coadministration of nevirapine and LEXIVA without ritonavir is not recommended. No dosage adjustment required when nevirapine is administered with LEXIVA/ritonavir twice daily. The combination of nevirapine administered with LEXIVA/ritonavir once-daily regimen has not been studied.
HIV protease inhibitor: Atazanavir ^a	LEXIVA: Interaction has not	Appropriate doses of the combinations with respect to safety and efficacy have

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

HIV CCR5 co-receptor antagonist: Maraviroc ^a	LEXIVA/ritonavir: ↓Amprenavir ↑Maraviroc	No dosage adjustment required for LEXIVA/ritonavir. The recommended dose of maraviroc is 150 mg twice daily when coadministered with LEXIVA/ritonavir. LEXIVA should be given with ritonavir when coadministered with maraviroc.
<i>Other Agents</i>		
Antiarrhythmics: Amiodarone, bepridil, lidocaine (systemic), and quinidine	↑Antiarrhythmics	Use with caution. Increased exposure may be associated with life-threatening reactions such as cardiac arrhythmias. Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin Phenytoin ^a	LEXIVA: ↓Amprenavir LEXIVA/ritonavir: ↑Amprenavir ↓Phenytoin	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Plasma phenytoin concentrations should be monitored and phenytoin dose should be increased as appropriate. No change in LEXIVA/ritonavir dose is recommended.
Antidepressant: Paroxetine, trazodone	↓Paroxetine ↑Trazodone	Coadministration of paroxetine with LEXIVA/ritonavir significantly decreased plasma levels of paroxetine. Any paroxetine dose adjustment should be guided by clinical effect (tolerability and efficacy). Concomitant use of trazodone and LEXIVA with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration

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

		<p>Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p> <p>LEXIVA and coadministration of colchicine:</p> <p>Treatment of gout flares: 1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg twice a day or 0.6 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once a day.</p> <p>Treatment of FMF: Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day).</p>
<p>Antimycobacterial: Rifabutin^a</p>	<p>↑Rifabutin and rifabutin metabolite</p>	<p>A complete blood count should be performed weekly and as clinically indicated to monitor for neutropenia.</p> <p>LEXIVA: A dosage reduction of rifabutin by at least half the recommended dose is required.</p> <p>LEXIVA/ritonavir: Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).</p>
<p>Antipsychotics: Quetiapine</p>	<p>LEXIVA/ritonavir: ↑Quetiapine</p>	<p><u>Initiation of LEXIVA with ritonavir in patients taking quetiapine:</u> Consider alternative antiretroviral therapy to avoid increases in quetiapine drug</p>

		<p>exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring.</p> <p><u>Initiation of quetiapine in patients taking LEXIVA with ritonavir:</u> Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.</p>
<p>Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam</p>	<p>↑Benzodiazepines</p>	<p>Clinical significance is unknown. A decrease in benzodiazepine dose may be needed.</p>
<p>Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine</p>	<p>↑Calcium channel blockers</p>	<p>Use with caution. Clinical monitoring of patients is recommended.</p>
<p>Corticosteroid: Dexamethasone</p>	<p>↓Amprenavir</p>	<p>Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations.</p>
<p>Endothelin-receptor antagonists: Bosentan</p>	<p>↑Bosentan</p>	<p>Coadministration of bosentan in patients on LEXIVA:</p> <p>In patients who have been receiving LEXIVA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p> <p>Coadministration of LEXIVA in patients on bosentan:</p> <p>Discontinue use of bosentan at least 36 hours prior to initiation of LEXIVA.</p> <p>After at least 10 days following the</p>

		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.

<p>Narcotic analgesic: Methadone</p>	<p>↓Methadone</p>	<p>Data suggest that the interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms.</p>
<p>Oral contraceptives: Ethinyl estradiol/ norethindrone^a</p>	<p>LEXIVA: ↓Amprenavir ↓Ethinyl estradiol</p> <p>LEXIVA/ritonavir: ↓Ethinyl estradiol</p>	<p>Alternative methods of non-hormonal contraception are recommended.</p> <p>May lead to loss of virologic response.^a</p> <p>Increased risk of transaminase elevations. No data are available on the use of LEXIVA/ritonavir with other hormonal therapies, such as hormone replacement therapy (HRT) for postmenopausal women.</p>
<p>PDE5 inhibitors: Sildenafil, tadalafil, vardenafil</p>	<p>↑Sildenafil ↑Tadalafil ↑Vardenafil</p>	<p>May result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, 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></p> <p>In patients receiving LEXIVA for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Coadministration of LEXIVA in</u></p>

		<p><u>patients on ADCIRCA:</u> Avoid use of ADCIRCA during the initiation of LEXIVA. Stop ADCIRCA at least 24 hours prior to starting LEXIVA. After at least one week following the initiation of LEXIVA, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Use of PDE5 inhibitors for erectile dysfunction:</u></p> <p>LEXIVA: Sildenafil: 25 mg every 48 hours. Tadalafil: no more than 10 mg every 72 hours. Vardenafil: no more than 2.5 mg every 24 hours.</p> <p>LEXIVA/ritonavir: Sildenafil: 25 mg every 48 hours. Tadalafil: no more than 10 mg every 72 hours. Vardenafil: no more than 2.5 mg every 72 hours. Use with increased monitoring for adverse events.</p>
<p>Proton pump inhibitors: Esomeprazole^a, lansoprazole, omeprazole, pantoprazole, rabeprazole</p>	<p>LEXIVA: ↔Amprenavir ↑Esomeprazole</p> <p>LEXIVA/ritonavir: ↔Amprenavir ↔Esomeprazole</p>	<p>Proton pump inhibitors can be administered at the same time as a dose of LEXIVA with no change in plasma amprenavir concentrations.</p>
<p>Tricyclic antidepressants: Amitriptyline, imipramine</p>	<p>↑Tricyclics</p>	<p>Therapeutic concentration monitoring is recommended for tricyclic antidepressants.</p>

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

296 **8 USE IN SPECIFIC POPULATIONS**

297 **8.1 Pregnancy**

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

310 The mating and fertility of the F_1 generation born to female rats given fosamprenavir was not
311 different from control animals; however, fosamprenavir did cause a reduction in both pup
312 survival and body weights. Surviving F_1 female rats showed an increased time to successful
313 mating, an increased length of gestation, a reduced number of uterine implantation sites per litter,
314 and reduced gestational body weights compared with control animals. Systemic exposure
315 ($AUC_{0-24\text{ h}}$) to amprenavir in the F_0 pregnant rats was approximately 2 times higher than
316 exposures in humans following administration of the MRHD of fosamprenavir alone or
317 approximately the same as those seen in humans following administration of the MRHD of
318 fosamprenavir in combination with ritonavir.

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

321 Antiretroviral Pregnancy Registry

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

325 **8.3 Nursing Mothers**

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

331 **8.4 Pediatric Use**

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

339 Treatment with LEXIVA is not recommended in protease inhibitor-experienced pediatric
340 patients younger than 6 months. The pharmacokinetics, safety, tolerability, and efficacy of
341 LEXIVA in pediatric patients younger than 4 weeks have not been established [see *Clinical*
342 *Pharmacology (12.3)*]. Available pharmacokinetic and clinical data do not support once-daily
343 dosing of LEXIVA alone or in combination with ritonavir for any pediatrics or twice-daily
344 dosing without ritonavir in pediatric patients younger than 2 years [see *Clinical Pharmacology*
345 *(12.3)*, *Clinical Studies (14.3)*]. See *Dosage and Administration (2.2)* for dosing
346 recommendations for pediatric patients.

347 **8.5 Geriatric Use**

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

352 **8.6 Hepatic Impairment**

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

358 There are no data to support dosing recommendations for pediatric subjects with hepatic
359 impairment.

360 **10 OVERDOSAGE**

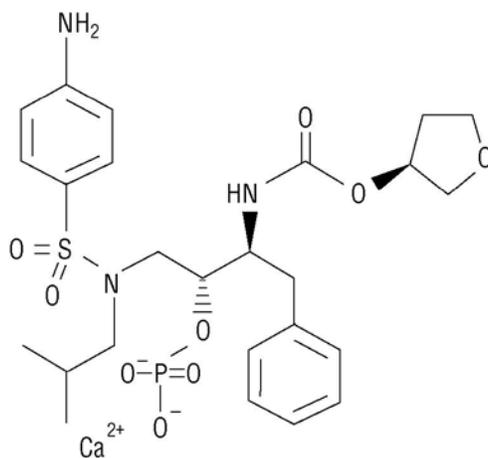
361 In a healthy volunteer repeat-dose pharmacokinetic trial evaluating high-dose combinations of
362 LEXIVA plus ritonavir, an increased frequency of Grade 2/3 ALT elevations (greater than 2.5 x
363 ULN) was observed with LEXIVA 1,400 mg twice daily plus ritonavir 200 mg twice daily (4 of
364 25 subjects).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

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

369 11 DESCRIPTION

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

376



377

378

379 Fosamprenavir calcium is a white to cream-colored solid with a solubility of approximately
380 0.31 mg per mL in water at 25°C.

381 LEXIVA tablets are available for oral administration in a strength of 700 mg of fosamprenavir as
382 fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir). Each 700 mg tablet
383 contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium
384 stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating contains the
385 inactive ingredients hypromellose, iron oxide red, titanium dioxide, and 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 without
397 ritonavir, have been evaluated in both healthy adult volunteers and in HIV-1-infected subjects;
398 no substantial differences in steady-state amprenavir concentrations were observed between the
399 2 populations.

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

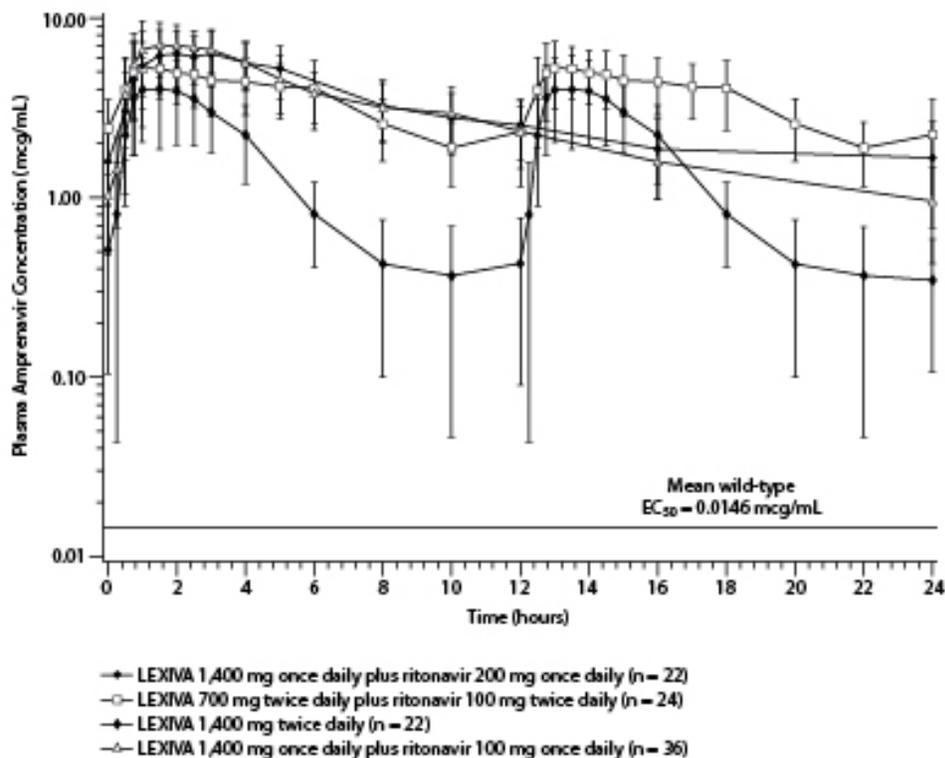
402 **Table 8. Geometric Mean (95% CI) Steady-state Plasma Amprenavir Pharmacokinetic**
403 **Parameters in Adults**

Regimen	C_{max} (mcg/mL)	T_{max} (hours)^a	AUC₂₄ (mcg•h/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)

404 ^a Data shown are median (range).

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

407 **Figure 1. Mean (\pm SD) Steady-state Plasma Amprenavir Concentrations**
 408 **and Mean EC₅₀ Values against HIV from Protease Inhibitor-naive**
 409 **Subjects (in the Absence of Human Serum)**



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

429 Distribution

430 In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to α_1 -acid
431 glycoprotein. In vitro, concentration-dependent binding was observed over the concentration
432 range of 1 to 10 mcg per mL, with decreased binding at higher concentrations. The partitioning
433 of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase,
434 reflecting the higher amount of unbound drug at higher concentrations.

435 Metabolism

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

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

443 Elimination

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

450 Special Populations

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

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

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

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

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

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

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

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

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

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

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

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

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

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

507 Drug Interactions

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

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

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

518 drugs on amprenavir) and Table 12 (effect of LEXIVA on other drugs). In addition, since
519 LEXIVA delivers comparable amprenavir plasma concentrations as AGENERASE, drug
520 interaction data derived from trials with AGENERASE are provided in Tables 11 and 13. For
521 information regarding clinical recommendations, [*see Drug Interactions (7)*].

522 **Table 10. Drug Interactions: Pharmacokinetic Parameters for Amprenavir after**
 523 **Administration of LEXIVA in the Presence of the Coadministered Drug(s)**

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

Ketoconazole ^d 200 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 days	15	↔	↔	↔
Lopinavir/ritonavir 533 mg/133 mg b.i.d.	1,400 mg b.i.d. for 2 weeks	18	↓13 ^e	↓26 ^e	↓42 ^e
Lopinavir/ritonavir 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↓58 (↓42 to ↓70)	↓63 (↓51 to ↓72)	↓65 (↓54 to ↓73)
Maraviroc 300 mg b.i.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	14	↓34 (↓25 to ↓41)	↓35 (↓29 to ↓41)	↓36 (↓27 to ↓43)
Maraviroc 300 mg q.d. for 10 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 20 days	14	↓29 (↓20 to ↓38)	↓30 (↓23 to ↓36)	↓15 (↓3 to ↓25)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	↔ ^c	↔ ^c	↔ ^c
Nevirapine 200 mg b.i.d. for 2 weeks ^f	1,400 mg b.i.d. for 2 weeks	17	↓25 (↓37 to ↓10)	↓33 (↓45 to ↓20)	↓35 (↓50 to ↓15)
Nevirapine 200 mg b.i.d. for 2 weeks ^f	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↔	↓11 (↓23 to ↑3)	↓19 (↓32 to ↓4)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	13	↔	↑20 (↑8 to ↑34)	↑19 (↑6 to ↑33)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg b.i.d. for 14 days (fasted)	14	↓27 (↓46 to ↔)	↓36 (↓53 to ↓13)	↓43 ^g (↓59 to ↓21)
	1,400 mg b.i.d. for 14 days ^h	14	↓15 (↓27 to ↓1)	↓17 (↓27 to ↓6)	↓32 ^g (↓53 to ↓1)
	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days (fasted)	14	↓14 (↓39 to ↑20)	↓17 (↓38 to ↑12)	↓20 ^g (↓45 to ↑17)

	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 14 days ^h	12	↓25 (↓42 to ↓2)	↓25 (↓44 to ↔)	↓33 ^g (↓52 to ↓7)
Raltegravir 400 mg b.i.d. for 14 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days (fasted)	13	↓18 (↓34 to ↔)	↓24 (↓41 to ↔)	↓50 ^g (↓64 to ↓31)
	1,400 mg q.d. plus ritonavir 100 mg q.d. for 14 days ^h	14	↑27 (↓1 to ↑62)	↑13 (↓7 to ↑38)	↓17 ^g (↓45 to ↑26)
Ranitidine 300 mg single dose (administered 1 hour before fosamprenavir)	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	↔ (↓19 to ↑21)
Rifabutin 150 mg q.o.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↑36 ^c (↑18 to ↑55)	↑35 ^c (↑17 to ↑56)	↑17 ^c (↓1 to ↑39)
Telaprevir 750 mg every 8 h for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	18	↓35 (↓30 to ↓41)	↓47 (↓42 to ↓51)	↓56 (↓50 to ↓60)
Telaprevir 1,125 mg every 12 h for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 24 days	17	↓40 ⁱ (↓33 to ↓45)	↓49 ⁱ (↓45 to ↓53)	↓58 ⁱ (↓53 to ↓63)
Tenofovir 300 mg q.d. for 4 to 48 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 to 48 weeks	45	NA	NA	↔ ^j
Tenofovir 300 mg q.d. for 4 to 48 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 4 to 48 weeks	60	NA	NA	↔ ^j

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

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

527 ^c Compared with historical control.

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

539 **Table 11. Drug Interactions: Pharmacokinetic Parameters for Amprenavir after**
540 **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

541 ^a Compared with parallel control group.

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

543 ^c Compared with historical data.

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

546 **Table 12. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the**
 547 **Presence of Amprenavir after Administration of LEXIVA**

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

Maraviroc 300 mg b.i.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	14	↑52 (↑27 to ↑82)	↑149 (↑119 to ↑182)	↑374 (↑303 to ↑457)
Maraviroc 300 mg q.d. for 10 days	1,400 mg q.d. plus ritonavir 100 mg q.d. for 20 days	14	↑45 (↑20 to ↑74)	↑126 (↑99 to ↑158)	↑80 (↑53 to ↑113)
Methadone 70 to 120 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	19	R-Methadone (active)		
			↓21 ^g (↓30 to ↓12)	↓18 ^g (↓27 to ↓8)	↓11 ^g (↓21 to ↑1)
			S-Methadone (inactive)		
			↓43 ^g (↓49 to ↓37)	↓43 ^g (↓50 to ↓36)	↓41 ^g (↓49 to ↓31)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	1,400 mg b.i.d. for 2 weeks	17	↑25 (↑14 to ↑37)	↑29 (↑19 to ↑40)	↑34 (↑20 to ↑49)
Nevirapine 200 mg b.i.d. for 2 weeks ^h	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↑13 (↑3 to ↑24)	↑14 (↑5 to ↑24)	↑22 (↑9 to ↑35)
Norethindrone ^c 0.5 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓38 (↓32 to ↓44)	↓34 (↓30 to ↓37)	↓26 (↓20 to ↓32)
Phenytoin 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	14	↓20 (↓12 to ↓27)	↓22 (↓17 to ↓27)	↓29 (↓23 to ↓34)
Rifabutin 150 mg every other day for 2 weeks ⁱ (25-O-desacetylriofabutin metabolite) 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
Telaprevir 750 mg every 8 h for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 20 days	18	↓33 (↓29 to ↓37)	↓32 (↓28 to ↓37)	↓30 (↓23 to ↓36)

- 548 ^a Concomitant medication is also shown in this column where appropriate.
- 549 ^b Comparison arm of atazanavir 300 mg q.d. plus ritonavir 100 mg q.d. for 10 days.
- 550 ^c Administered as a combination oral contraceptive tablet: ethinyl estradiol
- 551 0.035 mg/norethindrone 0.5 mg.
- 552 ^d Subjects were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with
- 553 both ketoconazole and LEXIVA/ritonavir.
- 554 ^e Data represent lopinavir concentrations.
- 555 ^f Compared with lopinavir 400 mg/ritonavir 100 mg b.i.d. for 2 weeks.
- 556 ^g Dose normalized to methadone 100 mg. The unbound concentration of the active moiety,
- 557 R-methadone, was unchanged.
- 558 ^h Subjects were receiving nevirapine for at least 12 weeks prior to trial.
- 559 ⁱ Comparison arm of rifabutin 300 mg q.d. for 2 weeks. AUC is AUC_(0-48 h).
- 560 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ less than 10%); ND = Interaction cannot be
- 561 determined as C_{min} was below the lower limit of quantitation.

562 **Table 13. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in**

563 **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

564 ^a Compared with historical data.

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

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

569 12.4 Microbiology

570 Mechanism of Action

571 Fosamprenavir is a prodrug that is rapidly hydrolyzed to amprenavir by cellular phosphatases in
572 the gut epithelium as it is absorbed. Amprenavir is an inhibitor of HIV-1 protease. Amprenavir
573 binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and
574 Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral
575 particles.

576 Antiviral Activity

577 Fosamprenavir has little or no antiviral activity in cell culture. The antiviral activity of
578 amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected
579 lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes in cell
580 culture. The 50% effective concentration (EC₅₀) of amprenavir ranged from 0.012 to
581 0.08 microM in acutely infected cells and was 0.41 microM in chronically infected cells
582 (1 microM = 0.50 mcg per mL). The median EC₅₀ value of amprenavir against HIV-1 isolates
583 from clades A to G was 0.00095 microM in peripheral blood mononuclear cells (PBMCs).
584 Similarly, the EC₅₀ values for amprenavir against monocytes/macrophage tropic HIV-1 isolates
585 (clade B) ranged from 0.003 to 0.075 microM in monocyte/macrophage cultures. The EC₅₀
586 values of amprenavir against HIV-2 isolates grown in PBMCs were higher than those for HIV-1
587 isolates, and ranged from 0.003 to 0.11 microM. Amprenavir exhibited synergistic anti-HIV-1
588 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir,
589 didanosine, lamivudine, stavudine, tenofovir, and zidovudine; the non-nucleoside reverse
590 transcriptase inhibitors (NNRTIs) delavirdine and efavirenz; and the protease inhibitors
591 atazanavir and saquinavir. Amprenavir exhibited additive anti-HIV-1 activity in combination
592 with the NNRTI nevirapine, the protease inhibitors indinavir, lopinavir, nelfinavir, and ritonavir;
593 and the fusion inhibitor enfuvirtide. These drug combinations have not been adequately studied
594 in humans.

595 Resistance

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

615 these resistant substitutions were traced back to Week 84 (76 weeks prior to clinical virologic
616 failure).

617 Cross-resistance

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

629 **Table 14. Responders at Trial Week 48 by Presence of Baseline Protease Inhibitor**
630 **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%

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

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

634 The virologic response based upon baseline phenotype was assessed. Baseline isolates from
635 protease inhibitor-experienced subjects responding to LEXIVA/ritonavir twice daily had a
636 median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of
637 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a
638 median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient

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

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

648 **13 NONCLINICAL TOXICOLOGY**

649 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

672 The effects of fosamprenavir on fertility and general reproductive performance were investigated
673 in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks before mating
674 through postpartum day 6). Systemic exposures (AUC_{0-24h}) to amprenavir in these studies were 3
675 (males) to 4 (females) times higher than exposures in humans following administration of the

676 MRHD of fosamprenavir alone or similar to those seen in humans following administration of
 677 fosamprenavir in combination with ritonavir. Fosamprenavir did not impair mating or fertility of
 678 male or female rats and did not affect the development and maturation of sperm from treated
 679 rats.

680 **14 CLINICAL STUDIES**

681 **14.1 Therapy-naive Adult Trials**

682 APV30001

683 A randomized, open-label trial evaluated treatment with LEXIVA tablets (1,400 mg twice daily)
 684 versus nelfinavir (1,250 mg twice daily) in 249 antiretroviral treatment-naive subjects. Both
 685 groups of subjects also received abacavir (300 mg twice daily) and lamivudine (150 mg twice
 686 daily).

687 The mean age of the subjects in this trial was 37 years (range: 17 to 70 years); 69% of the
 688 subjects were male, 20% were CDC Class C (AIDS), 24% were white, 32% were black, and 44%
 689 were Hispanic. At baseline, the median CD4+ cell count was 212 cells per mm³ (range: 2 to
 690 1,136 cells per mm³; 18% of subjects had a CD4+ cell count of less than 50 cells per mm³ and
 691 30% were in the range of 50 to less than 200 cells per mm³). Baseline median HIV-1 RNA was
 692 4.83 log₁₀ copies per mL (range: 1.69 to 7.41 log₁₀ copies per mL; 45% of subjects had greater
 693 than 100,000 copies per mL).

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

695 **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%

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

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

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

702 **Table 16. Proportions of Responders through Week 48 by Screening Viral Load**
703 **(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

704 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were
705 201 cells per mm³ in the group receiving LEXIVA and 216 cells per mm³ in the nelfinavir group.

706 APV30002

707 A randomized, open-label trial evaluated treatment with LEXIVA tablets (1,400 mg once daily)
708 plus ritonavir (200 mg once daily) versus nelfinavir (1,250 mg twice daily) in
709 649 treatment-naïve subjects. Both treatment groups also received abacavir (300 mg twice daily)
710 and lamivudine (150 mg twice daily).

711 The mean age of the subjects in this trial was 37 years (range: 18 to 69 years); 73% of the
712 subjects were male, 22% were CDC Class C, 53% were white, 36% were black, and 8% were
713 Hispanic. At baseline, the median CD4+ cell count was 170 cells per mm³ (range: 1 to
714 1,055 cells per mm³; 20% of subjects had a CD4+ cell count of less than 50 cells per mm³ and
715 35% were in the range of 50 to less than 200 cells per mm³). Baseline median HIV-1 RNA was
716 4.81 log₁₀ copies per mL (range: 2.65 to 7.29 log₁₀ copies per mL; 43% of subjects had greater
717 than 100,000 copies per mL).

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

719 **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.	Nelfinavir 1,250 mg b.i.d.
	(n = 322)	(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%

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

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

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

726 **Table 18. Proportions of Responders through Week 48 by Screening Viral Load**
727 **(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

728 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were
729 203 cells per mm³ in the group receiving LEXIVA and 207 cells per mm³ in the nelfinavir group.

730 **14.2 Protease Inhibitor-experienced Adult Trials**

731 APV30003

732 A randomized, open-label, multicenter trial evaluated 2 different regimens of LEXIVA plus
733 ritonavir (LEXIVA tablets 700 mg twice daily plus ritonavir 100 mg twice daily or LEXIVA
734 tablets 1,400 mg once daily plus ritonavir 200 mg once daily) versus lopinavir/ritonavir
735 (400 mg/100 mg twice daily) in 315 subjects who had experienced virologic failure to 1 or
736 2 prior protease inhibitor-containing regimens.

737 The mean age of the subjects in this trial was 42 years (range: 24 to 72 years); 85% were male,
738 33% were CDC Class C, 67% were white, 24% were black, and 9% were Hispanic. The median
739 CD4+ cell count at baseline was 263 cells per mm³ (range: 2 to 1,171 cells per mm³). Baseline

740 median plasma HIV-1 RNA level was 4.14 log₁₀ copies per mL (range: 1.69 to 6.41 log₁₀ copies
741 per mL).

742 The median durations of prior exposure to NRTIs were 257 weeks for subjects receiving
743 LEXIVA/ritonavir twice daily (79% had greater than or equal to 3 prior NRTIs) and 210 weeks
744 for subjects receiving lopinavir/ritonavir (64% had greater than or equal to 3 prior NRTIs). The
745 median durations of prior exposure to protease inhibitors were 149 weeks for subjects receiving
746 LEXIVA/ritonavir twice daily (49% received greater than or equal to 2 prior protease inhibitors)
747 and 130 weeks for subjects receiving lopinavir/ritonavir (40% received greater than or equal to
748 2 prior protease inhibitors).

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

752 The proportions of subjects who achieved and maintained confirmed HIV-1 RNA less than
753 400 copies per mL (secondary efficacy endpoint) were 58% with twice-daily LEXIVA/ritonavir
754 and 61% with lopinavir/ritonavir (95% CI for the difference: -16.6, 10.1). The proportions of
755 subjects with HIV-1 RNA less than 50 copies per mL with twice-daily LEXIVA/ritonavir and
756 with lopinavir/ritonavir were 46% and 50%, respectively (95% CI for the difference: -18.3, 8.9).
757 The proportions of subjects who were virologic failures were 29% with twice-daily
758 LEXIVA/ritonavir and 27% with lopinavir/ritonavir.

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

761 Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were
762 81 cells per mm³ with twice-daily LEXIVA/ritonavir and 91 cells per mm³ with
763 lopinavir/ritonavir.

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

766 Once-daily administration of LEXIVA plus ritonavir is not recommended for protease
767 inhibitor-experienced patients. Through Week 48, 50% and 37% of subjects receiving LEXIVA
768 1,400 mg plus ritonavir 200 mg once daily had plasma HIV-1 RNA less than 400 copies per mL
769 and less than 50 copies per mL, respectively.

770 **14.3 Pediatric Trials**

771 Three open-label trials in pediatric subjects aged at least 4 weeks to 18 years were conducted. In
772 one trial (APV29005), twice-daily dosing regimens (LEXIVA with or without ritonavir) were
773 evaluated in combination with other antiretroviral agents in pediatric subjects aged 2 to 18 years.
774 In a second trial (APV20002), twice-daily dosing regimens (LEXIVA with ritonavir) were
775 evaluated in combination with other antiretroviral agents in pediatric subjects aged at least
776 4 weeks to less than 2 years. A third trial (APV20003) evaluated once-daily dosing of LEXIVA

777 with ritonavir; the pharmacokinetic data from this trial did not support a once-daily dosing
778 regimen in any pediatric patient population.

779 APV29005

780 *LEXIVA*: Twenty (18 therapy-naive and 2 therapy-experienced) pediatric subjects received
781 *LEXIVA* oral suspension without ritonavir twice daily. At Week 24, 65% (13 of 20) achieved
782 HIV-1 RNA less than 400 copies per mL, and the median increase from baseline in CD4+ cell
783 count was 350 cells per mm³.

784 *LEXIVA plus Ritonavir*: Forty-nine protease inhibitor-naive and 40 protease
785 inhibitor-experienced pediatric subjects received *LEXIVA* oral suspension or tablets with
786 ritonavir twice daily. At Week 24, 71% of protease inhibitor-naive (35 of 49) and 55% of
787 protease inhibitor-experienced (22 of 40) subjects achieved HIV-1 RNA less than 400 copies per
788 mL; median increases from baseline in CD4+ cell counts were 184 cells per mm³ and 150 cells
789 per mm³ in protease inhibitor-naive and experienced subjects, respectively.

790 APV20002

791 Fifty-four pediatric subjects (49 protease inhibitor-naive and 5 protease inhibitor-experienced)
792 received *LEXIVA* oral suspension with ritonavir twice daily. At Week 24, 72% of subjects
793 achieved HIV-1 RNA less than 400 copies per mL. The median increases from baseline in CD4+
794 cell counts were 400 cells per mm³ in subjects aged at least 4 weeks to less than 6 months and
795 278 cells per mm³ in subjects aged 6 months to 2 years.

796 **16 HOW SUPPLIED/STORAGE AND HANDLING**

797 *LEXIVA* tablets, 700 mg, are pink, film-coated, capsule-shaped, biconvex tablets, with
798 “GX LL7” debossed on one face.

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

800 Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to
801 86°F) (see USP Controlled Room Temperature). Keep container tightly closed.

802 *LEXIVA* oral suspension, a white to off-white grape-bubblegum-peppermint-flavored
803 suspension, contains 50 mg of fosamprenavir as fosamprenavir calcium equivalent to
804 approximately 43 mg of amprenavir in each 1 mL.

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

806 This product does not require reconstitution.

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

809 **17 PATIENT COUNSELING INFORMATION**

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

811 **17.1 Drug Interactions**

812 A statement to patients and healthcare providers is included on the product's bottle label:

813 **ALERT:** Find out about medicines that should NOT be taken with LEXIVA.

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

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

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

823 **17.2 Sulfa Allergy**

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

826 **17.3 Redistribution/Accumulation of Body Fat**

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

830 **17.4 Information about Therapy with LEXIVA**

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

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

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

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

850 **17.5 Oral Suspension**

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

853

854 LEXIVA and AGENERASE are registered trademarks of the ViiV Healthcare group of
855 companies.

856 The other brands listed are trademarks of their respective owners and are not trademarks of the
857 ViiV Healthcare group of companies. The makers of these brands are not affiliated with and do
858 not endorse the ViiV Healthcare group of companies or its products.

859

860

861 Manufactured for:



ViiV Healthcare
Research Triangle Park, NC 27709



Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

862

863 by:



GlaxoSmithKline

864

865 GlaxoSmithKline

866 Research Triangle Park, NC 27709

867

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869 LXV: 1XPI

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871 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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PATIENT INFORMATION

LEXIVA[®] (lex-EE-vah) (fosamprenavir calcium) tablets and oral suspension

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

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

887 **What is LEXIVA?**

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

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

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

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

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

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

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

- 905 • **Do not share needles or other injection equipment.**
- 906 • **Do not share personal items that can have blood or body fluids on them,**
907 **like toothbrushes and razor blades.**

908 • **Do not have any kind of sex without protection.** Always practice safe sex
909 by using a latex or polyurethane condom to lower the chance of sexual contact
910 with semen, vaginal secretions, or blood.

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

913 **Who should not take LEXIVA?**

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

- 915 • alfuzosin (UROXATRAL[®])
- 916 • flecainide (TAMBOCOR[™])
- 917 • propafenone (RYTHMOL SR[®])
- 918 • rifampin (RIFADIN[®], RIFAMATE[®], RIFATER[®], RIMACTANE[®])
- 919 • ergot including:
 - 920 • dihydroergotamine mesylate (D.H.E. 45[®], MIGRANAL[®])
 - 921 • ergotamine tartrate (CAFERGOT[®], MIGERGOT[®], ERGOMAR[®], MEDIHALER
 - 922 ERGOTAMINE[®])
 - 923 • methylergonovine (METHERGINE[®])
- 924 • St. John's wort (*Hypericum perforatum*)
- 925 • lovastatin (ADVICOR[®], ALTOPREV[®], MEVACOR[®])
- 926 • simvastatin (ZOCOR[®], VYTORIN[®], SIMCOR[®])
- 927 • pimozide (ORAP[®])
- 928 • delavirdine mesylate (RESCRIPTOR[®])
- 929 • sildenafil (REVATIO[®]), for treatment of pulmonary arterial hypertension
- 930 • triazolam (HALCION[®])

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

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

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

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

- 938 • are allergic to medicines that contain sulfa

- 939 • have liver problems, including hepatitis B or C
- 940 • have kidney problems
- 941 • have high blood sugar (diabetes)
- 942 • have hemophilia
- 943 • have any other medical condition
- 944 • are pregnant or plan to become pregnant. It is not known if LEXIVA will harm
- 945 your unborn baby.

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

- 950 • **Do not breastfeed.** We do not know if LEXIVA can be passed to your baby in
951 your breast milk and whether it could harm your baby. Also, mothers with HIV-1
952 should not breastfeed because HIV-1 can be passed to the baby in the breast
953 milk.

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

957 Taking LEXIVA with certain other medicines may cause serious side effects. LEXIVA
958 may affect the way other medicines work, and other medicines may affect how
959 LEXIVA works.

960 Especially tell your healthcare provider if you take:

- 961 • quetiapine (SEROQUEL[®])
- 962 • estrogen-based contraceptives (birth control pills). LEXIVA may reduce
963 effectiveness of estrogen-based contraceptives. During treatment with LEXIVA,
964 you should use a different contraceptive method.

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

967 **How should I take LEXIVA?**

- 968 • **Stay under the care of a healthcare provider while taking LEXIVA.**
- 969 • Take LEXIVA exactly as prescribed by your healthcare provider.
- 970 • Do not change your dose or stop taking LEXIVA without talking with your
971 healthcare provider.

- 972 • If your child is taking LEXIVA, your child's healthcare provider will decide the
973 right dose based on your child's weight.
- 974 • You can take LEXIVA tablets with or without food.
- 975 • **Adults should take LEXIVA oral suspension without food.**
- 976 • **Children should take LEXIVA oral suspension with food.** If your child
977 vomits within 30 minutes after taking a dose of LEXIVA, the dose should be
978 repeated.
- 979 • Shake LEXIVA oral suspension well before each use.
- 980 • If you miss a dose of LEXIVA, take the next dose as soon as possible and then
981 take your next dose at the regular time. Do not double the next dose. If you take
982 too much LEXIVA, call your healthcare provider or go to the nearest hospital
983 emergency room right away.

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

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

- 986 • **Severe skin rash.** LEXIVA may cause severe or life-threatening skin reactions
987 or rash.

988 **If you get a rash with any of the following symptoms, stop taking** 989 **LEXIVA and call your healthcare provider or get medical help right** 990 **away:**

- 991 • hives or sores in your mouth, or your skin blisters and peels
- 992 • trouble swallowing or breathing
- 993 • swelling of your face, eyes, lips, tongue, or throat
- 994 • **Liver problems.** Your healthcare provider should do blood tests before and
995 during your treatment with LEXIVA to check your liver function. Some people
996 with liver problems, including hepatitis B or C, may have an increased risk of
997 developing worsening liver problem during treatment with LEXIVA.
- 998 • **Diabetes and high blood sugar (hyperglycemia).** Some people who take
999 protease inhibitors, including LEXIVA, can get high blood sugar, develop
1000 diabetes, or your diabetes can get worse. Tell your healthcare provider if you
1001 notice an increase in thirst or urinate often while taking LEXIVA.
- 1002 • **Changes in your immune system (Immune Reconstitution Syndrome)** can
1003 happen when you start taking HIV medicines. Your immune system may get
1004 stronger and begin to fight infections that have been hidden in your body for a

1005 long time. Call your healthcare provider right away if you start having new
1006 symptoms after starting your HIV medicine.

1007 • **Changes in body fat.** These changes can happen in people who take
1008 antiretroviral therapy. The changes may include an increased amount of fat in
1009 the upper back and neck (“buffalo hump”), breast, and around the back, chest,
1010 and stomach area. Loss of fat from the legs, arms, and face may also happen.
1011 The exact cause and long-term health effects of these conditions are not known.

1012 • **Changes in blood tests.** Some people have changes in blood tests while taking
1013 LEXIVA. These include increases seen in liver function tests, blood fat levels, and
1014 decreases in white blood cells. Your healthcare provider should do regular blood
1015 tests before and during your treatment with LEXIVA.

1016 • **Increased bleeding problems in some people with hemophilia.** Some
1017 people with hemophilia have increased bleeding with protease inhibitors,
1018 including LEXIVA.

1019 • **Kidney stones.** Some people have developed kidney stones while taking
1020 LEXIVA. Tell your healthcare provider right away if you develop signs or
1021 symptoms of kidney stones:

- 1022 • pain in your side
- 1023 • blood in your urine
- 1024 • pain when you urinate

1025 **The most common side effects of LEXIVA in adults include:**

- 1026 • nausea
- 1027 • vomiting
- 1028 • diarrhea
- 1029 • headache

1030 Vomiting is the most common side effect in children when taking LEXIVA.

1031 Tell your healthcare provider about any side effect that bothers you or that does
1032 not go away.

1033 These are not all the possible side effects of LEXIVA. For more information, ask
1034 your healthcare provider or pharmacist.

1035 Call your doctor for medical advice about side effects. You may report side effects
1036 to FDA at 1-800-FDA-1088.

1037 **How should I store LEXIVA?**

- 1038 • Store LEXIVA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- 1039 • Keep the bottle of LEXIVA tablets tightly closed.
- 1040 • Store LEXIVA oral suspension between 41°F to 86°F (5°C to 30°C). Refrigeration
- 1041 of LEXIVA oral suspension may improve taste for some people.
- 1042 • Do not freeze.

1043 **Keep LEXIVA and all medicines out of the reach of children.**

1044 **General information about LEXIVA**

1045 Medicines are sometimes prescribed for purposes other than those listed in a
1046 Patient Information leaflet. Do not use LEXIVA for a condition for which it was not
1047 prescribed. Do not give LEXIVA to other people, even if they have the same
1048 symptoms you have. It may harm them.

1049 This leaflet summarizes the most important information about LEXIVA. If you would
1050 like more information, talk with your healthcare provider. You can ask your
1051 pharmacist or healthcare provider for information about LEXIVA that is written for
1052 health professionals.

1053 For more information call 877-844-8872 or go to www.LEXIVA.com.

1054 **What are the ingredients in LEXIVA?**

1055 **Tablets:**

1056 **Active ingredient:** fosamprenavir calcium

1057 **Inactive ingredients:** colloidal silicon dioxide, croscarmellose sodium, magnesium
1058 stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating
1059 contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and
1060 triacetin.

1061 **Oral Suspension:**

1062 **Active ingredient:** fosamprenavir calcium

1063 **Inactive ingredients:** artificial grape-bubblegum flavor, calcium chloride
1064 dihydrate, hypromellose, methylparaben, natural peppermint flavor, polysorbate
1065 80, propylene glycol, propylparaben, purified water, and sucralose.

1066 This Patient Information has been approved by the U.S. Food and Drug
1067 Administration.

1068 LEXIVA and AGENERASE are registered trademarks of the ViiV Healthcare group of
1069 companies.

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