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LEXIVA

Fosamprenavir (as fosamprenavir calcium)
Film Coated Tablets

1 INDICATIONS AND USAGE

LEXIVA is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults.

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

- The protease inhibitor-experienced patient trial was not large enough to reach a definitive conclusion that LEXIVA plus ritonavir and lopinavir plus ritonavir are clinically equivalent *[see Clinical Studies (13.2)]*.
- Once-daily administration of LEXIVA plus ritonavir is not recommended for adult protease inhibitor-experienced patients *[see Dosage and Administration (2.2), Clinical Studies (13.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

LEXIVA tablets may be taken with or without food.

Higher-than-approved dose combinations of LEXIVA plus ritonavir are not recommended due to an increased risk of transaminase elevations *[see Overdosage (9)]*.

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

2.2 Adults

Therapy-Naive Adults

- LEXIVA 1,400 mg twice daily (without ritonavir).
- LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily.
- LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily.
    - Dosing of LEXIVA 1,400 mg once daily plus ritonavir 100 mg once daily is supported by pharmacokinetic data *[see Clinical Pharmacology (11.2)]*.
- LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily.

- Dosing of LEXIVA 700 mg twice daily plus 100 mg ritonavir twice daily is supported by pharmacokinetic and safety data *[see Clinical Pharmacology (11.2)]*.

Protease Inhibitor-Experienced Adults:

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

2.3 **Patients with Hepatic Impairment**

See Clinical Pharmacology (11.2).

Unboosted (without ritonavir)

Mild to Moderate Hepatic Impairment (Child-Pugh Score Ranging from 5 to 9)

LEXIVA tablets should be used with caution at a reduced dosage of 700 mg twice daily in therapy-naïve patients.

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

LEXIVA tablets should not be used in patients with severe hepatic impairment because adequate dosage reduction cannot be achieved.

Boosted (with ritonavir)

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

LEXIVA should be used with caution and at a reduced dosage of 700 mg twice daily with 100 mg ritonavir once daily (therapy-naïve or protease inhibitor-experienced patients).

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

LEXIVA tablets should not be used with ritonavir in patients with moderate hepatic impairment because adequate dosage reduction cannot be achieved.

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

LEXIVA tablets must not be used with ritonavir in patients with severe hepatic impairment because adequate dosage reduction cannot be achieved.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

LEXIVA is contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome) to any of the components of this product or to amprenavir.
- when coadministered with drugs that are highly dependent on cytochrome P450 3A4 (CYP3A4) for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (Table 1).

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

Drug Class/Drug Name	Clinical Comment
Alpha 1-adrenoreceptor antagonists: 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.
Antipsychotics: Lurasidone	**POTENTIAL** for serious and/or life-threatening reactions if LEXIVA is co-administered with **ritonavir**.
Antipsychotics: Pimozide	**POTENTIAL** for serious and/or life-threatening reactions such as cardiac arrhythmias.

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 (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
HMG CoA-reductase inhibitors: Lovastatin, simvastatin	**POTENTIAL** for serious reactions such as risk of myopathy including rhabdomyolysis.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine[a]	May lead to loss of virologic response and possible resistance to delavirdine.
PDE5 inhibitors: 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.

[a] *See Clinical Pharmacology (11.2) Tables 8, 9, 10, or 11 for magnitude of interaction.*

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

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

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

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

See Table 6 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during therapy with LEXIVA/ritonavir; review concomitant medications during therapy with LEXIVA/ritonavir; and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4), Drug Interactions (7)]*.

5.2 Skin Reactions

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

5.3 Sulfa Allergy

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

5.4 Hepatic Toxicity

Use of LEXIVA with ritonavir at higher-than-recommended dosages may result in transaminase elevations and should not be used *[see Dosage and Administration (2), Overdosage (9)]*. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing or worsening of transaminase elevations. Appropriate laboratory testing should be conducted prior to initiating therapy with LEXIVA and patients should be monitored closely during treatment.

5.5 Diabetes/Hyperglycemia

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

5.6 Immune Reconstitution Syndrome

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

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

5.7 Increase in Body Fat

Increased of body fathas been observed in patients receivingprotease inhibitors, including LEXIVA. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.8 Lipid Elevations

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

5.9 Hemolytic Anemia

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

5.10 Patients with Hemophilia

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

5.11 Nephrolithiasis

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

5.12 Resistance/Cross-Resistance

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect therapy with LEXIVA will have on the activity of

subsequently administered protease inhibitors. LEXIVA has been studied in patients who have experienced treatment failure with protease inhibitors *[see Clinical Studies (13.2)]*.

6 ADVERSE REACTIONS

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

6.1 Clinical Trials

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

Adult Trials

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

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

Table 2. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater than or Equal to 2% of Antiretroviral-Naive Adult Subjects

	APV30001[a]		APV30002[a]	
Adverse Reaction	**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%

[a] All subjects also received abacavir and lamivudine twice daily.

Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater than or 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%

[a] All subjects also received 2 reverse transcriptase inhibitors.

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

less than 1% of subjects. In some subjects with mild or moderate rash, dosing with LEXIVA was often continued without interruption; if interrupted, reintroduction of LEXIVA generally did not result in rash recurrence.

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

Table 4. Grade 3/4 Laboratory Abnormalities Reported in Greater than or Equal to 2% of Antiretroviral-Naive Adult Subjects in Trials APV30001 and APV30002

	APV30001[a]		**APV30002[a]**	
Laboratory Abnormality	**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%

[a] All subjects also received abacavir and lamivudine twice daily.

[b] Fasting specimens.

ULN = Upper limit of normal.

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

Table 5. Grade 3/4 Laboratory Abnormalities Reported in Greater than or Equal to 2% of 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]

[a] All subjects also received 2 reverse transcriptase inhibitors.

[b] Fasting specimens.

[c] n = 100 for LEXIVA plus ritonavir, n = 98 for lopinavir plus ritonavir.

ULN = Upper limit of normal.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LEXIVA. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to LEXIVA.

Cardiac Disorders

Myocardial infarction.

Metabolism and Nutrition Disorders

Hypercholesterolemia.

Nervous System Disorders

Oral paresthesia.

Skin and Subcutaneous Tissue Disorders

Angioedema.

Urogenital

Nephrolithiasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any

suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il). Additionally, you should also report to GSK Israel (il.safety@gsk.com).

7 DRUG INTERACTIONS

See also Contraindications (4), Clinical Pharmacology (11.2).

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

7.1 Cytochrome P450 Inhibitors and Inducers

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

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

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

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

7.2 Drugs that Should Not Be Coadministered with LEXIVA

See Contraindications (4).

7.3 Established and Other Potentially Significant Drug Interactions

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

Table 6. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HCV/HIV-Antiviral Agents		
HCV protease inhibitor: Boceprevir	**LEXIVA** ↓Amprenavir (predicted) ↔ or ↓Boceprevir (predicted) **LEXIVA/ritonavir:** ↓Amprenavir (predicted) ↓Boceprevir (predicted)	Coadministration of LEXIVA or LEXIVA/ritonavir and boceprevir is not recommended.
HCV protease inhibitor: Simeprevir	**LEXIVA:** ↔Amprenavir (predicted) ↑ or ↓Simeprevir (predicted) **LEXIVA/ritonavir:** ↔Amprenavir (predicted) ↑Simeprevir (predicted)	Coadministration of LEXIVA or LEXIVA/ritonavir and simeprevir is not recommended.
HCV protease inhibitor: Paritaprevir (coformulated with ritonavir and ombitasvir and coadministered with dasabuvir)	**LEXIVA:** ↑Amprenavir (predicted) ↑ or ↔Paritaprevir (predicted) **LEXIVA/ritonavir:** ↑ or ↔Amprenavir (predicted) ↑Paritaprevir	Appropriate doses of the combinations with respect to safety and efficacy have not been established. LEXIVA 1,400 mg once daily may be considered when coadministered with paritaprevir/ritonavir/ombitasvir/ dasabuvir. Coadministration of LEXIVA/ritonavir and paritaprevir/ritonavir/ombitasvir/

	(predicted)	dasabuvir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	**LEXIVA:** ↓Amprenavir **LEXIVA/ritonavir:** ↓Amprenavir	For contraindicated NNRTIs (delavirdine), *[see Contraindications (4)]*. 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	For contraindicated NNRTIs (delavirdine), *[see Contraindications (4)]*. Coadministration of nevirapine and LEXIVA without ritonavir is not recommended. No dosage adjustment required when nevirapine is administered with LEXIVA/ritonavir twice daily. The combination of nevirapine administered with LEXIVA/ritonavir once-daily regimen has not been studied.
HIV protease inhibitor: Atazanavir[a]	**LEXIVA:** Interaction has not been evaluated. **LEXIVA/ritonavir:** ↓Atazanavir ↔Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Indinavir[a], nelfinavir[a]	**LEXIVA:** ↑Amprenavir Effect on indinavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.

	and nelfinavir is not well established. **LEXIVA/ritonavir:** Interaction has not been evaluated.	
HIV protease inhibitors: Lopinavir/ritonavir[a]	↓Amprenavir ↓Lopinavir	An increased rate of adverse events has been observed. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Saquinavir[a]	**LEXIVA:** ↓Amprenavir Effect on saquinavir is not well established. **LEXIVA/ritonavir:** Interaction has not been evaluated.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
HIV integrase inhibitor: Raltegravir[a]	**LEXIVA:** ↓Amprenavir ↓Raltegravir **LEXIVA/ritonavir:** ↓Amprenavir ↓Raltegravir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
HIV integrase inhibitor: Dolutegravir[a]	**LEXIVA/ritonavir:** ↓Dolutegravir	The recommended dose of dolutegravir is 50 mg twice daily when coadministered with LEXIVA/ritonavir. Use an alternative combination where possible in patients with known or suspected integrase inhibitor resistance.

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.
Other Agents		
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	↑Antiarrhythmics	For contraindicated antiarrhythmics (flecainide, propafenone), *[see Contraindications (4)]*. 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	Any paroxetine dose adjustment should be guided by clinical effect (tolerability and efficacy). 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):** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).

		LEXIVA and coadministration of colchicine: **Treatment of gout flares:** 1.2 mg (2 tablets) x 1 dose. 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 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. **Treatment of FMF:** Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day).
Antimycobacterial: Rifabutin[a]	↑Rifabutin and rifabutin metabolite	For contraindicated antimycobacterials (rifampin), *[see Contraindications (4)]*. A complete blood count should be performed weekly and as clinically indicated to monitor for neutropenia. **LEXIVA:** A dosage reduction of rifabutin by at least half the recommended dose is required. **LEXIVA/ritonavir:** Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).
Antipsychotics: Quetiapine	**LEXIVA/ritonavir:** ↑Quetiapine	For contraindicated antipsychotics (lurasidone, pimozide), *[see Contraindications (4)]*.

Lurasidone	↑Lurasidone	<u>Initiation of LEXIVA with ritonavir in patients taking quetiapine:</u> Consider alternative antiretroviral therapy to avoid increases in quetiapine drug 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. <u>Initiation of quetiapine in patients taking LEXIVA with ritonavir:</u> Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine. **LEXIVA:** If coadministration is necessary, reduce the lurasidone dose. Refer to the lurasidone prescribing information for concomitant use with moderate CYP3A4 inhibitors. **LEXIVA/ritonavir**: Use of lurasidone is contraindicated.
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑Benzodiazepines	For contraindicated sedative/hypnotics (midazolam, triazolam), *[see Contraindications (4)]*. Clinical significance is unknown. A decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine,	↑Calcium channel blockers	Use with caution. Clinical monitoring of patients is recommended.

isradipine		
Corticosteroid: Dexamethasone	↓Amprenavir	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations.
Endothelin-receptor antagonists: Bosentan	↑Bosentan	Coadministration of bosentan in patients on LEXIVA: In patients who have been receiving LEXIVA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Coadministration of LEXIVA in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of LEXIVA. After at least 10 days following the initiation of LEXIVA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Histamine H_2-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	For contraindicated HMG-CoA reductase inhibitors (lovastatin, simvastatin), *[see Contraindications (4)]*. Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed atorvastatin 20 mg/day.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus	↑Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents.
Inhaled beta-agonist: Salmeterol	↑Salmeterol	Concurrent administration of salmeterol with LEXIVA is not recommended. The combination may result in increased risk of cardiovascular adverse events

		associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Inhaled/nasal steroid: Fluticasone	**LEXIVA:** ↑Fluticasone **LEXIVA/ritonavir:** ↑Fluticasone	Use with caution. Consider alternatives to fluticasone, particularly for long-term use. May result in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone. Coadministration of fluticasone and LEXIVA/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
Narcotic analgesic: Methadone	↓Methadone	Data suggest that the interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms.
Oral contraceptives: Ethinyl estradiol/ norethindrone[a]	**LEXIVA:** ↓Amprenavir ↓Ethinyl estradiol **LEXIVA/ritonavir:** ↓Ethinyl estradiol	Alternative methods of non-hormonal contraception are recommended. May lead to loss of virologic response.[a] Increased risk of transaminase elevations. No data are available on the use of LEXIVA/ritonavir with other hormonal therapies, such as hormone replacement therapy (HRT) for postmenopausal women.
PDE5 inhibitors: Sildenafil, tadalafil, vardenafil	↑Sildenafil ↑Tadalafil ↑Vardenafil	For contraindicated PDE5 inhibitors [sildenafil (REVATIO)], *[see Contraindications (4)]*. May result in an increase in PDE5

		inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism. Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): • Use of sildenafil is contraindicated when used for the treatment of PAH *[see Contraindications (4)]*. • The following dose adjustments are recommended for use of tadalafil with LEXIVA: Coadministration of tadalafil in patients on LEXIVA: In patients receiving LEXIVA for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Coadministration of LEXIVA in patients on tadalafil: Avoid use of tadalafil during the initiation of LEXIVA. Stop tadalafil at least 24 hours prior to starting LEXIVA. After at least one week following the initiation of LEXIVA, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE5 inhibitors for erectile dysfunction: **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.

		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.
Proton pump inhibitors: Esomeprazole[a], lansoprazole, omeprazole, pantoprazole, rabeprazole	**LEXIVA:** ↔Amprenavir ↑Esomeprazole **LEXIVA/ritonavir:** ↔Amprenavir ↔Esomeprazole	Proton pump inhibitors can be administered at the same time as a dose of LEXIVA with no change in plasma amprenavir concentrations.
Tricyclic antidepressants: Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants.

[a] *See Clinical Pharmacology (11.2) Tables 8, 9, 10, or 11 for magnitude of interaction.*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) to adequately assess the risk of adverse developmental outcomes. Fosamprenavir use during pregnancy has been evaluated in a limited number of women as reported by the APR. Available data from the APR show 2 birth defects in 109 first trimester exposures and 2 birth defects in 36 second and third trimester exposures compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The estimated rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population evaluates women and infants from a limited geographic area, and does not include birth defects in pregnancy outcomes for births that occurred at less than 20 weeks' gestation.

In animal reproduction studies, no evidence of major adverse developmental outcomes was observed following oral administration of fosamprenavir. Systemic exposure to amprenavir (the

active ingredient) was less than (rabbits) or up to 2 times (rats) those in humans at the maximum recommended human dose (MRHD) with or without ritonavir. In contrast, oral administration of amprenavir was associated with abortions in pregnant rabbits at doses that produced approximately one-twentieth the human exposure at the MRHD.

In the rat pre- and post-natal development study, toxicities to the offspring, including reduced survival and reproductive performance, were observed at maternal systemic exposures (AUC) to amprenavir that were approximately 2 times the exposure in humans at the MRHD of fosamprenavir alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir in combination with ritonavir *(see Data).*

Data

Human Data: Based on prospective reports to the APR of approximately 146 live births following exposure to fosamprenavir-containing regimens (including 109 live births exposed in the first trimester and 36 live births exposed in the second and third trimesters) there were 4 birth defects reported in live-born infants.

Animal Data: Fosamprenavir was administered orally to pregnant rats (300, 820, or 2,240 mg per kg per day) and rabbits (74.8, 224.3, or 672.8 mg per kg per day) on gestation Days 6 to 17 and Days 7 to 20, respectively. No major adverse effects on embryo-fetal development were observed at these dose levels, resulting in exposures ($AUC_{0\text{-}24\ h}$) approximately 2 times (rats) and 0.8 times (rabbits) human exposures at the MRHD of fosamprenavir alone or 0.7 times (rats) and 0.3 times (rabbits) human exposures at the MRHD of fosamprenavir in combination with ritonavir. However, increased incidence of abortion was observed in rabbits administered a maternally toxic dose of fosamprenavir (672.8 mg per kg per day). In a study where amprenavir was administered orally to pregnant rabbits (25, 50, or 100 mg per kg per day) on gestation Days 8 to 20, increased abortions and an increased incidence of minor skeletal variations (deficient ossification of the femur, humerus, and trochlea) were observed at doses that produced approximately one-twentieth the exposure seen at the MRHD.

In the rat pre- and post-natal development study, fosamprenavir was administered orally (300, 820, or 2,240 mg per kg per day) on gestation Day 6 to lactation/post-partum Day 20. Fosamprenavir caused a reduction in pup survival and body weights. In surviving female offspring from the high-dose group, an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights were observed. Systemic exposure ($AUC_{0\text{-}24\ h}$) to amprenavir in rats was approximately 2 times the exposures in humans at the MRHD of fosamprenavir alone or approximately the same as those seen in humans at the MRHD of fosamprenavir in combination with ritonavir.

8.2 Lactation

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

There is no information available on the presence of amprenavir in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. When administered to lactating rats, amprenavir was present in milk *(see Data)*. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving LEXIVA.

Data

Amprenavir was excreted into the milk of lactating rats following a single dose of amprenavir (100 mg per kg); a maximal milk concentration was achieved 2 hours post-administration at a milk concentration approximately 1.2 times that of maternal plasma concentrations.

8.3 Females and Males of Reproductive Potential

Contraception

Use of LEXIVA may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

8.3 Pediatric Use

Lexiva tablets are only approved for adult use.

8.4 Geriatric Use

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

8.5 Hepatic Impairment

Amprenavir is principally metabolized by the liver; therefore, caution should be exercised when administering LEXIVA to patients with hepatic impairment because amprenavir concentrations may be increased *[see Clinical Pharmacology (11.2)]*. Patients with impaired hepatic function receiving LEXIVA with or without concurrent ritonavir require dose reduction *[see Dosage and Administration (2.3)]*.

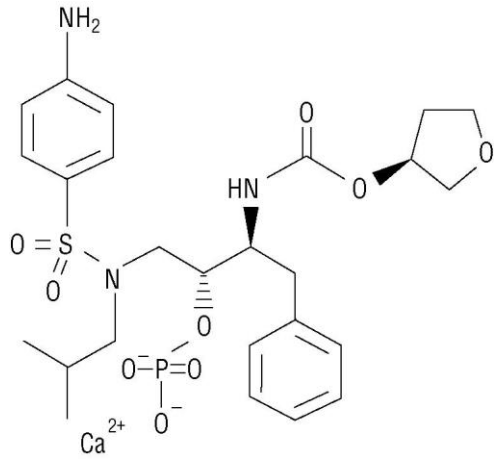
9 OVERDOSAGE

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

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

10 DESCRIPTION

LEXIVA (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of HIV protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-[[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$ and a molecular weight of 623.7. It has the following structural formula:



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

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

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Fosamprenavir is an antiretroviral agent *[see Microbiology (11.3)]*.

11.2 Pharmacokinetics

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

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

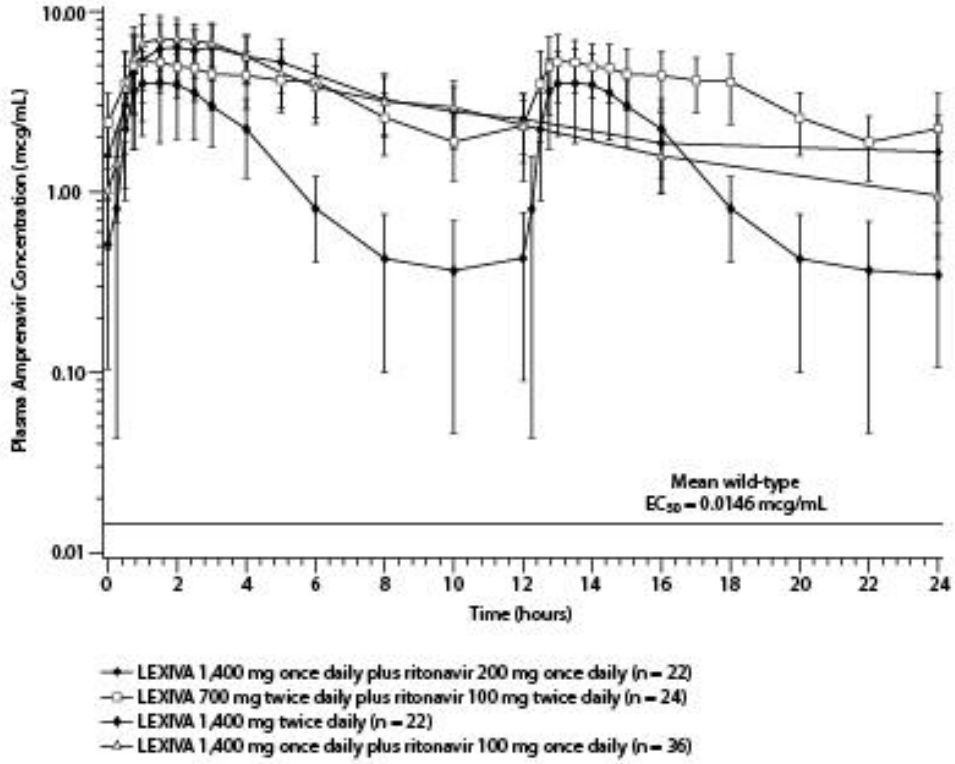
Table 7. Geometric Mean (95% CI) Steady-state Plasma Amprenavir Pharmacokinetic Parameters in Adults

Regimen	C_{max} (mcg/mL)	T_{max} (hours)[a]	AUC_{24} (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)

[a] Data shown are median (range).

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

Figure 1. Mean (±SD) Steady-state Plasma Amprenavir Concentrations and Mean EC_{50} Values against HIV from Protease Inhibitor-Naive Subjects (in the Absence of Human Serum)



Absorption

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

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

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

Effects of Food on Oral Absorption

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

the fasted state was associated with no significant changes in amprenavir C_{max}, T_{max}, or $AUC_{0-\infty}$ *[see Dosage and Administration (2)]*.

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

Distribution

In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to $alpha_1$-acid glycoprotein. In vitro, concentration-dependent binding was observed over the concentration range of 1 to 10 mcg per mL, with decreased binding at higher concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism

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

Elimination

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

Specefic Populations

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

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

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

Geriatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to patients older than 65 years have not been studied *[see Use in Specific Populations (8.4)]*.

Male and Female Patients: The pharmacokinetics of amprenavir after administration of LEXIVA do not differ between males and females.

Racial Groups: The pharmacokinetics of amprenavir after administration of LEXIVA do not differ between blacks and non-blacks.

Drug Interaction Studies

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

Amprenavir, the active metabolite of fosamprenavir, is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Data also suggest that amprenavir induces CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT). Amprenavir is both a substrate for and inducer of P-glycoprotein.

Drug interaction trials were performed with LEXIVA and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration on AUC, C_{max}, and C_{min} values are summarized in Table 8 (effect of other drugs on amprenavir) and Table 10 (effect of LEXIVA on other drugs). In addition, since LEXIVA delivers comparable amprenavir plasma concentrations as AGENERASE, drug interaction data derived from trials with AGENERASE are provided in Tables 9 and 11. For information regarding clinical recommendations, *[see Drug Interactions (7)]*.

Table 8. Drug Interactions: Pharmacokinetic Parameters for Amprenavir after 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)
Tenofovir 300 mg q.d. for 4 to 48 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 to 48 weeks	45	NA	NA	↔[i]
Tenofovir 300 mg q.d. for 4 to 48 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 4 to 48 weeks	60	NA	NA	↔[i]

[a] Concomitant medication is also shown in this column where appropriate.

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

[c] Compared with historical control.

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

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

[f] Subjects were receiving nevirapine for at least 12 weeks prior to trial.

[g] C_{last} ($C_{12\,h}$ or $C_{24\,h}$).

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

[i] Compared with parallel control group.

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

Table 9. Drug Interactions: Pharmacokinetic Parameters for Amprenavir after 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

[a] Compared with parallel control group.

[b] Median percent change; confidence interval not reported.

[c] Compared with historical data.

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

Table 10. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the 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
Dolutegravir 50 mg q.d.	700 mg b.i.d. plus ritonavir 100 mg b.i.d.	12	↓24 (↓8 to ↓37)	↓35 (↓22 to ↓46)	↓49 (↓37 to ↓59)
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-desacetylrifabutin metabolite) Rifabutin + 25-O-desacetylrifabutin 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

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

Table 11. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in 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

[a] Compared with historical data.

[b] Median percent change; confidence interval not reported.

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

11.3 Microbiology

Mechanism of Action

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

Antiviral Activity

Fosamprenavir has little or no antiviral activity in cell culture. The antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes in cell culture. The 50% effective concentration (EC_{50}) of amprenavir ranged from 0.012 to 0.08 microM in acutely infected cells and was 0.41 microM in chronically infected cells (1 microM = 0.50 mcg per mL). The median EC_{50} value of amprenavir against HIV-1 isolates from clades A to G was 0.00095 microM in peripheral blood mononuclear cells (PBMCs). Similarly, the EC_{50} values for amprenavir against monocytes/macrophage tropic HIV-1 isolates (clade B) ranged from 0.003 to 0.075 microM in monocyte/macrophage cultures. The EC_{50} values of amprenavir against HIV-2 isolates grown in PBMCs were higher than those for HIV-1 isolates, and ranged from 0.003 to 0.11 microM. The anti–HIV–1 activity of amprenavir was not antagonistic in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and efavirenz and nevirapine; protease inhibitors (PIs) atazanavir,, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir and the gp41 fusion inhibitor enfuvirtide. These drug combinations have not been adequately studied in humans.

Resistance

HIV-1 isolates with decreased susceptibility to amprenavir have been selected in cell culture and obtained from subjects treated with fosamprenavir. Genotypic analysis of isolates from treatment-naive subjects failing amprenavir-containing regimens showed substitutions in the HIV-1 protease resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as substitutions in the p7/p1 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. Some of these amprenavir resistance-associated substitutions have also been detected in HIV-1 isolates from antiretroviral-naive subjects treated with LEXIVA. Of the 488 antiretroviral-naive subjects treated with LEXIVA 1,400 mg twice daily or LEXIVA 1,400 mg plus ritonavir 200 mg once daily in Trials APV30001 and APV30002, respectively, isolated from 61 subjects (29 receiving LEXIVA and 32 receiving LEXIVA/ritonavir) with virologic failure (plasma HIV-1 RNA greater than 1,000 copies per mL on 2 occasions on or after Week 12) were genotyped. Isolated from 5 of the 29 antiretroviral-naive subjects (17%) receiving LEXIVA without ritonavir in Trial APV30001 had evidence of genotypic resistance to amprenavir: I54L/M (n = 2), I54L + L33F (n = 1), V32I + I47V (n = 1), and M46I + I47V (n = 1). No amprenavir resistance-associated

substitutions were detected in isolated from antiretroviral-naive subjects treated with LEXIVA/ritonavir for 48 weeks in Trial APV30002. However, the M46I and I50V substitutions were detected in isolates from 1 virologic failure subject receiving LEXIVA/ritonavir once daily at Week 160 (HIV-1 RNA greater than 500 copies per mL). Upon retrospective analysis of stored samples using an ultrasensitive assay, these resistant substitutions were traced back to Week 84 (76 weeks prior to clinical virologic failure).

Cross-Resistance

Varying degrees of cross-resistance among HIV-1 protease inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1 RNA level less than 400 copies per mL) and protease inhibitor-resistance substitutions detected in baseline HIV-1 isolates from protease inhibitor-experienced subjects receiving LEXIVA/ritonavir twice daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in Trial APV30003 is shown in Table 12. The majority of subjects had previously received either one (47%) or 2 protease inhibitors (36%), most commonly nelfinavir (57%) and indinavir (53%). Out of 102 subjects with baseline phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (n = 55) had resistance to at least one protease inhibitor, with 98% (n = 54) of those having resistance to nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60% (n = 58) had resistance to at least one protease inhibitor, with 97% (n = 56) of those having resistance to nelfinavir.

Table 12. Responders at Trial Week 48 by Presence of Baseline Protease Inhibitor 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%

[a] Results should be interpreted with caution because the subgroups were small.

[b] Most subjects had greater than 1 protease inhibitor resistance-associated substitution at baseline.

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

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

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

The effects of fosamprenavir on fertility and general reproductive performance were investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks before mating through postpartum Day 6) that received doses of 300, 820, or 2,240 mg per kg per day. Systemic exposures ($AUC_{0\text{-}24\ h}$) to amprenavir in these studies were 3 (males) to 4 (females) times higher than exposures in humans following administration of the MRHD of fosamprenavir alone or similar to those seen in humans following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

13 CLINICAL STUDIES

13.1 Therapy-Naive Adult Trials

APV30001

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

The mean age of the subjects in this trial was 37 years (range: 17 to 70 years); 69% of the subjects were male, 20% were CDC Class C (AIDS), 24% were white, 32% were black, and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells per mm^3 (range: 2 to 1,136 cells per mm^3; 18% of subjects had a CD4+ cell count of less than 50 cells per mm^3 and 30% were in the range of 50 to less than 200 cells per mm^3). Baseline median HIV-1 RNA was 4.83 log_{10} copies per mL (range: 1.69 to 7.41 log_{10} copies per mL; 45% of subjects had greater than 100,000 copies per mL).

The outcomes of randomized treatment are provided in Table 13.

Table 13. 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%

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

[b] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other reasons.

Treatment response by viral load strata is shown in Table 14.

Table 14. Proportions of Responders through Week 48 by Screening Viral Load (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

Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 201 cells per mm^3 in the group receiving LEXIVA and 216 cells per mm^3 in the nelfinavir group.

APV30002

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

The mean age of the subjects in this trial was 37 years (range: 18 to 69 years); 73% of the subjects were male, 22% were CDC Class C, 53% were white, 36% were black, and 8% were Hispanic. At baseline, the median CD4+ cell count was 170 cells per mm^3 (range: 1 to 1,055 cells per mm^3; 20% of subjects had a CD4+ cell count of less than 50 cells per mm^3 and 35% were in the range of 50 to less than 200 cells per mm^3). Baseline median HIV-1 RNA was 4.81 $\log_{10}$ copies per mL (range: 2.65 to 7.29 $\log_{10}$ copies per mL; 43% of subjects had greater than 100,000 copies per mL).

The outcomes of randomized treatment are provided in Table 15.

Table 15. Outcomes of Randomized Treatment through Week 48 (APV30002)

Outcome (Rebound or discontinuation = failure)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d. (n = 322)	Nelfinavir 1,250 mg b.i.d. (n = 327)
Responder[a]	69% (58%)	68% (55%)
Virologic failure	6%	16%
Rebound	5%	8%

Never suppressed through Week 48	1%	8%
Death	1%	0%
Discontinued due to adverse reactions	9%	6%
Discontinued due to other reasons[b]	15%	10%

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

[b] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other reasons.

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

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

Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 203 cells per mm^3 in the group receiving LEXIVA and 207 cells per mm^3 in the nelfinavir group.

13.2 Protease Inhibitor-Experienced Adult Trials

APV30003

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

The mean age of the subjects in this trial was 42 years (range: 24 to 72 years); 85% were male, 33% were CDC Class C, 67% were white, 24% were black, and 9% were Hispanic. The median CD4+ cell count at baseline was 263 cells per mm^3 (range: 2 to 1,171 cells per mm^3). Baseline median plasma HIV-1 RNA level was 4.14 $\log_{10}$ copies per mL (range: 1.69 to 6.41 $\log_{10}$ copies per mL).

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

and 130 weeks for subjects receiving lopinavir/ritonavir (40% received greater than or equal to 2 prior protease inhibitors).

The time-averaged changes in plasma HIV-1 RNA from baseline (AAUCMB) at 48 weeks (the endpoint on which the trial was powered) were -1.4 $\log_{10}$ copies per mL for twice-daily LEXIVA/ritonavir and -1.67 $\log_{10}$ copies per mL for the lopinavir/ritonavir group.

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

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

Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 81 cells per mm^3 with twice-daily LEXIVA/ritonavir and 91 cells per mm^3 with lopinavir/ritonavir.

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

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

14. HOW SUPPLIED/STORAGE AND HANDLING

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

Bottle of 60 with child-resistant closure.
Store below 30°C.
The expiry date of the product is indicated on the label and packaging.

16 MANUFACTURER: Glaxo Wellcome S.A., Burgos, Spain

17 LICENSE HOLDER AND IMPORTER: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

18 LICENSE NUMBER: 131-85-31013

Lex DR v10