## These highlights do not include all the information needed to use FOSAMPRENAVIR CALCIUM TABLETS safely and effectively. See full prescribing information for FOSAMPRENAVIR CALCIUM TABLETS.

FOSAMPRENAVIR CALCIUM tablets, for oral use Initial U.S. Approval: 2003 - RECENT MAJOR CHANGES --

Dosage and Administration, Adults (2.2) Contraindications (4) 03/2019 -- INDICATIONS AND USAGE --Fosamprenavir calcium tablet are HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

-- DOSAGE AND ADMINISTRATION --

Therapy-Naive Adults: Fosamprenavir calcium tablets 1,400 mg twice daily; fosamprenavir calcium tablets 1,400 mg once daily plus ritonavir 200 mg once daily; fosamprenavir calcium tablets 1,400 mg once daily plus ritonavir 100 mg once daily; fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily. (2.2) Protease Inhibitor-Experienced Adults: Fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily. (2.2)

Pregnant Palients: Fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily should only be considered in women who are already on a stable twice-daily regimen of fosamprenavir calcium /ritonavir 700 mg/100 mg prior to pregnancy and who are virologically suppressed (HIV-1 RNA less than 50 copies per mL). (2.2) Pediatric Patients (aged at least 4 weeks to 18 years): Dosage should be calculated based on body weight (kg) and should not exceed

Hepatic Impairment: Recommended adjustments for patients with mild, moderate, or severe hepatic impairment. (2.4) **Dosing Considerations** 

Fosamprenavir Calcium tablets may be taken with or without food. (2.1)
 Fosamprenavir Calcium Oral Suspension: Adults should take without food; pediatric patients should take with food. (2.1)

- DOSAGE FORMS AND STRENGTHS - 700 mg tablets (3) --- CONTRAINDICATIONS --

Hypersensitivity to fosamprenavir calcium or amprenavir (e.g., Stevens-Johnson syndrome). (4)

 Drugs highly dependent on cytochrome P450 (CYP)3A4 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) FULL PRESCRIBING INFORMATION: CONTENTS\*

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FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE

6.1 Clinical Trials Experience6.2 Postmarketing Experience

Fosamprenavir calcium tablets are indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection. The following points should be considered when initiating therapy with fosamprenavir calcium tablets plus ritonavir in protease inhibitor-experienced patients:

The protease inhibitor-experienced patient trial was not large enough to reach a definitive conclusion that fosamprenavir calcium tablets plus ritonavir and lopinavir plus ritonavir are clinically equivalent (see Clinical Studies (14.2)).

Once-daily administration of fosamprenavir calcium tablets plus ritonavir is not recommended for adult protease inhibitor-experienced patients or any pediatric patients (see Dosage and Administration (2.2, 2.3), Clinical Studies (14.2, 14.3).

Dosing of fosamprenavir calcium tablets plus ritonavir is not recommended for protease inhibitor-experienced pediatric patients younger than 6 months [see Clinical Pharmacology (12.3)].

2 DOSAGE AND ADMINISTRATION **2.1 General Dosing Information**Fosamprenavir calcium tablets may be taken with or without food. To sample name and unit autres may be calculated and a window to the date of t calcium oral suspension should occur. Higher-than-approved dose combinations of fosamprenavir calcium tablets plus ritonavir are not recommended due to an increased risk When fosamprenavir calcium tablets are used in combination with ritonavir, prescribers should consult the full prescribing information

2.2 Adults Therapy-Naive Adults Fosamprenavir calcium tablets 1,400 mg twice daily (without ritonavir).
Fosamprenavir calcium tablets 1,400 mg once daily plus ritonavir 200 mg once daily.
Fosamprenavir calcium tablets 1,400 mg once daily plus ritonavir 100 mg once daily.

o Dosing of fosamprenavir calcium tablets 1,400 mg once daily plus ritonavir 100 mg once daily is supported by pharmacokinetic data [see Clinical Pharmacology (12.3)].

 Fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily Dosing of fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily is supported by pharmacokinetic and safety data [see Clinical Pharmacology (12.3)].

Protease Inhibitor-Experienced Adults Fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily

Fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily rosamiprelawit caudini radies? You fing wice dairy plus intolawit You fly wice dairy, or obsing of fosamprenavir calcium tablets 700 mg twice daily plus ritonavir 100 mg twice daily should only be considered in pregnant patients who are already on a stable twice-daily regimen of fosamprenavir calcium /ritonavir 700 mg/100 mg prior to pregnancy and who are virologically suppressed (HIV-1 RIVA less than 50 copies per ml.). Lower exposures of amprenavir were observed during pregnancy, therefore, viral load should be monitored closely to ensure viral suppression is maintained /see Use in Specific Populations (8.1), Clinical Pharmacology (12.3). Data regarding use of other regimens of fosamprenavir calcium tablets (with or without ritonavir) in pregnancy are not available. 2.3 Pediatric Patients (Aged at Least 4 Weeks to 18 Years)

The recommended dosage of fosamprenavir calcium in patients aged at least 4 weeks to 18 years should be calculated based on body weight (kg) and should not exceed the recommended adult dose (Table 1). Table 1. Twice-Daily Dosage Regimens by Weight for Protease Inhibitor-Naive Pediatric Patients (Aged 4 Weeks) and Older) and for Protease Inhibitor-Experienced Pediatric Patients (Aged 6 Months and Older) Using Fosamprenavir Calcium Oral Suspension with Twice-Daily Dosage Regimen Weight Fosamprenavir Calcium 45 mg/kg plus Fosamprenavir Calcium 30 mg/kg plus ritonavir 3 mg/kg Fosamprenavir Calcium 23 mg/kg plus ritonavir 3 mg/kg 1 kg - < 15 kg Fosamprenavir Calcium 18 mg/kg plus ritonavir 3 mg/kg ≥ 20 kg

Alternatively, protease inhibitor-naive children aged 2 years and older can be administered fosamprenavir calcium (without ritonavir) 30 mg per kg twice daily Fosamprenavir calcium should only be administered to infants born at 38 weeks' gestation or greater and who have attained a postnatal age of 28 days. For pediatric patients, pharmacokinetic and clinical data: • do not support once-daily dosing of fosamprenavir calcium alone or in combination with ritonavir [see Clinical Studies (14.3)].

 do not support administration of fosamprenavir calcium alone or in combination with ritonavir for protease inhibitor-experienced children younger than 6 months [see Clinical Pharmacology (12.3)]. do not support twice-daily dosing of fosamprenavir calcium without ritonavir in pediatric patients younger than 2 years [see Clinical Pharmacology (12:3)].

Other Dosing Considerations When administered without ritonavir, the adult regimen of fosamprenavir calcium tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg.

When administered in combination with ritonavir, fosamprenavir calcium tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg. 2.4 Patients with Hepatic Impairment See Clinical Pharmacology (12.3). Mild Hepatic Impairment (Child-Pugh Score Ranging from 5 to 6)

Fosamprenavir calcium tablets should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or protease inhibitor-experienced). Moderate Hepatic Impairment (Child-Pugh Score Ranging from 7 to 9)
Fosamprenavir calcium tablets should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naive) or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or protease inhibitor-experienced). Severe Henatic Impairment (Child-Pugh Score Ranging from 10 to 15)

Fosamprenavir calcium tablets should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naive) or 300 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or protease inhibitor-experienced). There are no data to support dosing recommendations for pediatric patients with hepatic impairment. 3 DOSAGE FORMS AND STRENGTHS

Fosamprenavir calcium tablets, 700 mg, are pink colored, coated, oval-shaped tablets with "RJ47" imprinted on one side with black ink and plain on the other side.

4 CONTRAINDICATIONS Fosamprenavir calcium 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 amprenavi Tosamprenavir calcium is contraindicated when coadministered with drugs that are highly dependent on cytochrome P450 (CYP)3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs and other contraindicated drugs (which may lead to reduced efficacy of fosamprenavir calcium and possible resistance) are listed before see Drug Interactions (7), Clinical Pharmacology (7, 23), The list of contraindicated drugs applies to the use of fosamprenir calcium with or without ritonavir, unless otherwise indicated. If fosamprenavir calcium is coadministered with ritonavir, reference should be made to the full prescribing information for ritonavir for additional contraindications.

Fosamprenavir calcium is contraindicated when coadministered with the following drugs:

Alpha 1-adrenoreceptor antagonist: Alfuzosin Antiarrhythmics: Flecainide (with **ritonavir**), propafenone (with **ritonavir**)

Antimycobacterial: Rifampin
Antipsychotic: Lurasidone (with ritonavir), pimozide
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Gl motility agent: Cisapride
Herbal product: St. John's wort (Hypericum perforatum)
Lipid modifying agents: Lomitapide, lovastatin, simvastatin
Non-nucleoside reverse transcriptase inhibitor: Delavirdine
PDE5 inhibitor: Sildenafi (REVATIO) (for treatment of pulmonary arterial hypertension)
Cardinaliamporitic: Midrazlana trizonalam

5 WARNINGS AND PRECAUTIONS

Initiation of fosamorenavir calcium/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A, or initiation of medications metabolized by CYP3A in patients already receiving fosamprenavir calcii medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of fosamprenavir calcium/ritonavir, respectively. These interactions may lead to: clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of

clinically significant adverse reactions from greater exposures of fosamprenavir calcium/ritonavir loss of therapeutic effect of fosamprenavir calcium/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 fosamprenavir calcium/ritonavir, review concomitant medications during therapy with fosamprenavir calcium/ritonavir, and monitor for the adverse reactions associated with the concomitant medications [see Contraindications (4), Drug Interactions (7)].

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

Fosamprenavir calcium should be used with caution in patients with a known sulfonamide allergy. Fosamprenavir contains a sulfonamide molety. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown. In a clinical trial of fosamprenavir calcium 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 fosamprenavir calcium 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. 5.3 Sulfa Allergy

5.4 Hepatic Toxicity Use of fosamprenavir calcium with ritonavir at higher-than-recommended dosages may result in transaminase elevations and should not be used [see Dosage and Administration (2), Overdosage (10)]. Patients with underlying hepatitis 8 or C or marked elevations in transaminases prior to treatment may be at increased risk for developing or worsening of transaminase elevations. Overdosage (10) testing should be conducted prior to initiating therapy with fosamprenavir calcium 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 5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including fosamprenavir calcium. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic inflections (such as Mycobacterium avium infection, cytomegalovirus, Pneumorysis' inverse inpenumoia (PCP), or theoreulosis, 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 Increase of body fat has been observed in patients receiving protease inhibitors, including fosamprenavir calcium. 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 fosamprenavir calcium 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 fosamprenavir calcium and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate [see Drug Interactions (7)]. 5.9 Hemolytic Anemia

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 causa 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 fosamprenavir calcium. 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 fosamprenavir calcium will have on the activity of subsequently administered protease inhibitors. Fosamprenavir calcium has been studied in patients who have experienced treatment failure with protease inhibitors [see Clinical Studies (14.2)]. 6 ADVERSE REACTIONS Severe or life-threatening skin reactions have been reported with the use of fosamprenavir calcium [see Warnings and Precautions (5.2)].

 The most common moderate to severe adverse reactions in clinical trials of fosamprenavir calcium were diarrhea, rash, nausea, Treatment discontinuation due to adverse events occurred in 6.4% of subjects receiving fosamprenavir calcium and in 5.9% of subjects receiving comparator treatments. The most common adverse reactions leading to discontinuation of fosamprenavir cal (incidence less than or equal to 1% of subjects) included diarrhea, nausea, vomiting, AST increased, ALT increased, and rash. 6.1 Clinical Trials Experience

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 a nother 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 fosamprenavir calcium tablets, including 599 subjects exposed to fosamprenavir calcium 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 fosamprenavir calcium 1,400 mg once daily plus ritonavir 200 mg once daily, 24% received fosamprenavir calcium 1,400 mg twice daily nur ritonavir 100 mg twice daily.

Selected adverse reactions reported during the clinical efficacy trials of fosamprenavir calcium are shown in Tables 2 and 3. Each table Table 2. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater than or Equal to 2% of Antiretroviral-Naive Adult Subjects APV30001<sup>a</sup> APV30002<sup>a</sup>

Adverse Reaction	Fosamprenavir Calcium 1,400 mg Twice Daily (n = 166)	Nelfinavir 1,250 mg Twice Daily (n = 83)	Fosamprenavir Calcium 1,400 mg and Ritonavir 200 mg Once Daily (n = 322)	Nelfinavir 1,250 mg Twice Daily (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%

Table 3. Selected Moderate/Severe Clinical Adverse Reactions Reported in Greater than or Equal to 2% of Protease Inhibitor-

Adverse Reaction	Fosamprenavir Calcium 700 mg and Ritonavir 100 mg Twice Daily * (n = 106)	Lopinavir 400 mg and Ritonavir 100 mg Twice Daily <sup>a</sup> (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%

Skin rash (without regard to causality) occurred in approximately 19% of subjects treated with fosamprenavir calcium 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 initiation of fosamprenavir calcium and had a median duration of 13 days. Skin rash led to discontinuation of fosamprenavir calcium in less than 1% of subjects. In some subjects with mild or moderate rash, dosing with fosamprenavir calcium was often continued without

- WARNINGS AND PRECAUTIONS

 The concomitant use of fosamprenavir calcium 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, 7.2)
 Fosamprenavir calcium should be discontinued for severe skin reactions, including Stevens-Johnson syndrome. (5.2) Fosamprenavir calcium 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 fosamprenavir calcium may develop new onset or exacerbations of diabetes mellifus, hyperglycemia (5.5), immune reconstitution syndrome (5.6), increase 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

 Vomiting and neutropenia were more frequent in pediatrics than in adults. (6.1)
 To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA--- DRUG INTERACTIONS

 Coadministration of fosamprenavir calcium 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 fosampenavir calcium or fosamprenavir calcium and ritonavir may result in clinically significant interactions with drugs metabolized by CYP3A4. (7)

Coadministration of fosamprenavir calcium and ritonavir may result in clinically significant interactions with drugs metabolized by

--- USE IN SPECIFIC POPULATIONS Lactation: Breastfeeding is not recommended due to potential for HIV transmission. (8.2)

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

7 DRUG INTERACTIONS Cytochrome P450 Inhibitors and Inducers
Established and Other Potentially Significant Drug Interactions 8 USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential Geriatric Use 10 OVERDOSAGE 11 DESCRIPTION

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action12.3 Pharmacokinetics 13 NONCLINICAL TOXICOLOGY 14 CLINICAL STUDIES

14.1 Therapy-Naive Adult Trials
14.2 Protease Inhibitor-Experienced Adult Trials
14.3 Pediatric Trials 16 HOW SUPPLIED/STORAGE AND HANDLING 17 PATIENT COUNSELING INFORMATION

Sections or subsections omitted from the full prescribing information are not listed. interruption; if interrupted, reintroduction of fosamprenavir calcium generally did not result in rash recurrence. The percentages of subjects with Grade 3 or 4 laboratory abnormalities in the clinical efficacy trials of fosamprenavir calcium are presented

	APV3000	1ª	APV30002°		
	Fosamprenavir Calcium 1,400 mg Twice Daily (n = 166)	Nelfinavir 1,250 mg Twice Daily (n = 83)	Fosamprenavir Calcium 1,400 mg and Ritonavir 200 mg Once Daily	Nelfinavir 1,250 mg Twice Daily	
Laboratory Abnormality			(n = 322)	(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 <sup>b</sup> (> 750 mg/dL)	0%	1%	6%	2%	
Neutrophil count, absolute (< 750 cells/mm³)	3%	6%	3%	4%	

The incidence of Grade 3 or 4 hyperglycemia in antiretroviral-naive subjects who received fosamprenavir calcium in the pivotal trials was 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	Fosamprenavir Calcium 700 mg and Ritonavir 100 mg Twice Daily" (n = 104)	Lopinavir 400 mg and Ritonavir 100 mg Twice Daily <sup>a</sup> (n = 103)
Triglycerides <sup>b</sup> (> 750 mg/dL)	11%°	6%°
Serum lipase (> 2 x ULN)	5%	12%
ALT (> 5 x ULN)	4%	4%
AST (> 5 x ULN)	4%	2%
Glucose (> 251 mg/dL)	2%℃	2%°

Pediatric Trials

Fosamprenavir calcium with and without ritonavir was studied in 237 HIV-1-infected pediatric subjects aged at least 4 weeks to 18 years in 3 open-label trials; APV20002, APV20003, and APV29005 [see Clinical Studies (14.3)]. Vomiting and neutropenia occurred more frequently in pediatric subjects compared with adults. Other adverse events occurred with similar frequency in pediatric subjects compared with adults.

The frequency of vomiting among pediatric subjects receiving fosamprenavir calcium twice daily with ritonavir was 20% in subjects aged at least 4 weeks to younger than 2 years and 36% in subjects aged 2 to 18 years compared with 10% in adults. The frequency of vomiting among pediatric subjects receiving fosamprenavir calcium twice daily without ritonavir was 60% in subjects aged 2 to 5 years compare with 16% in adults. The median duration of drug-related vomiting episodes in APV29005 was 1 day (range: 1 to 3 days), in APV20003 was 16 days (range: 1 to 38 days), and in APV20002 was 9 days (range: 4 to 13 days). Vomiting was treatment limiting in 4 pediatric subjects across all 3 trials. The incidence of Grade 3 or 4 neutropenia (neutrophils less than 750 cells per mm<sup>3</sup>) seen in pediatric subjects treated with foragmenavir collisions with an district incidence and in adult subject (1904). Carda 2/4 neutropenia occurred in calcium with and without ritonavir was higher (15%) than the incidence seen in adult subjects (3%). Grade 3/4 neutropenia o 10% (5 of 51) of subjects aged at least 4 weeks to younger than 2 years and 16% (28 of 170) of subjects aged 2 to 18 years. 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fosamprenavir calcium. 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 These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal

Metabolism and Nutrition Disorders vous System Disorders n and Subcutaneous Tissue Disorders

7 DRUG INTERACTIONS

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

Amprenavir is metabolized by CYP3A4. Coadministration of fosamprenavir calcium and drugs that induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its therapeutic effect. Coadministration of fosamprenavir calcium and drugs that inhibit CYP3A4 may increase amprenavir concentrations and increase the incidence of adverse effects. The potential for drug interactions with fosamprenavir calcium changes when fosamprenavir calcium 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 fosamprenavir calcium is coadministered with ritonavir. Because ritonavir is a CYP2D6 inhibitor, clinically significant interactions with drugs metabolized by CYP2D6 are possible when coadministered with fosamprenavir calcium plus ritonavir. Ritonavir. intéractions with drugs metabolized by CYP2D6 are possible when coadministered with fosamprenavir calcium plus ritonavir. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6, as well as other enzymes, including glucuronosyl transferase. There are other agents that may result in serious and/or life-threatening drug interactions [see Contraindications (4)]. 7.2 Established and Other Potentially Significant Drug Interactions

If fosamprenavir calcium is used in combination with ritonavir, see full prescribing information for ritonavir for additional information on drug interactions [see Contraindications (4), Clinical Pharmacology (12.3)]. Table 6 provides a listing of established or potentially clinically significant drug interactions. Information in the table applies to fosamprenavir

Table 6. Established and Other Potentially Significant Drug Interactions Concomitant Drug Class: Effect on Concentration of Amprenavir or Concomitat Clinical Comment HCV/HIV-Antiviral Agents Fosamprenavir calcium nistration of fosamprenavir calciun or fosamprenavir calcium/ ritonavir and ↓ Amprenavi (predicted) oceprevir is not recommended. → or ↓ Boceprevi Fosamprenavir calciu ↓Amprenavi predicted) ↓Boceprevir HCV protease inhibitor: Fosamprenavir calcium → Amprenavir (predicted) meprevir is not recommended.

Coadministration of fosamprenavir calciun ↑ or ↓ Simeprevi (predicted) Fosamprenavir calcius /ritonavir: →Amprenavi (predicted) 'predicted' Appropriate doses of the combinations with **HCV** protease inhibitor Paritaprevir (coformulated respect to safety and efficacy have not been with ritonavir and Fosamprenavir calcium 1400 mg once daily ↑ or ↔Paritaprevi ombitasvir and may be considered when coadministered with paritaprevir/ritonavir/ombitasvir/ coadministered with predicted) dasabuvir) Fosamprenavir calciun Coadministration of Fosamprenavir calciung ↑ or ↔Amprenav (predicted) paritaprevir/ritonavir/ombitasvir/ dasabuvi is not recommended (predicted) Non-nucleoside reverse Fosamprenavir calcium Coadministration is contraindicated as it ranscriptase inhibitor may lead to loss of virologic response and Amprenavi Delavirdine possible resistance to delavirdine [see . Contraindications (4)]. Fosamprenavir calcium/ritonavi Amprenavir Delavirdine Non-nucleoside reverse Fosamprenavir calcium

Appropriate doses of the combinations with respect to safety and efficacy have not been Fosamprenavi An additional 100 mg/day (300 mg total) o calcium/ritonavir ritonavir is recommended when efavirenz is L Amprenavir dministered with fosamprenavir calcium /ritonavir once daily. No change in the administered with Fosamprenavir calcium Coadministration of nevirapine and Non-nucleoside reverse Fosamprenavir calcium fosamprenavir calcium without ritonavir i transcriptase inhibitor Nevirapine Fosamprenavi No dosage adjustment required when calcium/ritonavir: nevirapine is administered with fosamprenavir calcium/ritonavir twice daily. , Amprenavir ↑ Nevirapine The combination of nevirapine administered daily regimen has not been studied. Appropriate doses of the combinations with HIV protease inhibitor Fosamprenavir calcium Interaction has not been respect to safety and efficacy have not been evaluated. Fosamprenavir

Atazanavir → Amprenavi Fosamprenavir calcium Amprenavir respect to safety and efficacy have not beer Effect on indinavir and nelfinavir is not well established. calcium/ritonavir: Interaction

has not been evaluated. HIV protease inhibitors: An increased rate of adverse events has ↓ Amprenavi been observed. Appropriate doses of the combinations with respect to safety and efficacy have not been established HIV protease inhibitor Fosamorenavir calcium Appropriate doses of the combination with , Amprenavir respect to safety and efficacy have not been Effect on saguinavir is not well established Fosamprenavir calcium/ritonavir: Interaction has not been evaluated HIV integrase inhibitor: Appropriate doses of the combination with Fosamprenavir calcium ↓ Amprenaviı ↓ Raltegravir respect to safety and efficacy have not beer Fosamprenavir calcium/ritonavir Amprenavir

HIV integrase inhi Fosamprenavir calcium The recommended dose of dolutegravir is **ritonavir:** ↓Dolutegravir 50 mg twice daily when coadministered with Fosamprenavir calcium /ritonavir. Use an alternative combination where possible in patients with known or uspected integrase inhibitor resistance HIV CCR5 co-receptor Fosamprenavir No dosage adjustment required for fosamprenavir calcium /ritonavir. The L Amprenavir recommended dose of maraviroc is 150 mg twice daily when coadministered with fosamprenavir calcium/ritonavir

Fosamprenavir calcium should be give with ritonavir when coadministered with Other Agents Alpha 1-adrenorecepto Coadministration is contraindicated due to potential hypotension [see Contraindications (4)]. LAmprenavi lasma concentrations

MAALOX TC

Ethinyl estradiol/norethindrone ↓ Amprenavir Use with caution when administered at the same time. Fosamprenavir calcium may be less effective due to decreased amprenav Staggered coadministration of antacids and fosamprenavir calcium has not been

Fluticasone

Lipid Modifying Agents: HMG-CoA reductase

Concomitant Drug Class Effect on Concentration o Drug Name Amprenavir or Concomitan **Clinical Commen** Theraneutic concentration monitoring, if Antiarrhythmics: Antiarrhythmics Amiodarone, disopyramio available, is recommended for lidocaine (systemic), and Flecainide, propafenone Coadministration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias if fosamprenavir calcium is co-prescribed with ritonavir [see Contraindications (4)]. Concentrations of warfarin may be affected It is recommended that INR (international normalized ratio) be monitored.

Use with caution. Fosamprenavir calcium Fosamprenavir calcium Carbamazepine may be less effective due to decreased ↓ Amprenavir amprenavir plasma concentrations in patients taking these agents concomitantly Plasma phenytoin concentrations should b henytoin Fosamprenavi nonitored and phenytoin dose should be ↑ Amprenavir increased as appropriate. No change in Phenytoin fosamprenavir calcium/ritonavir dose is Any paroxetine dose adjustment should Antidepressant: Paroxetine 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 use with a CYP3A4 inhibitor such as fosamprenavir calcium, the combination should be used with caution and a lower dose of trazodone should be considered Increase monitoring for adverse events. Ketoconazol Ketoconazole<sup>3</sup> Itraconazole Fosamprenavir calcium: itraconazole Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole

auinidine

Anticoagulant:

Antimycobacterial

Antimycobacterial

Benzodiazepines:

diazepam, flurazepam

Warfarin

Revised: 05/2019

Anti-gout: ↑ Colchicine Patients with renal or hepatic impairment Colchicine should not be given colchicine with fosamprenavir calcium/ritonavir Fosamprenavir calcium/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 feve

(FMF):

or itraconazole per day.

Fosamprenavir calcium/ritonavi High doses of ketoconazole or itraconazole

(greater than 200 mg/day) are not

given as 0.3 mg twice a day Fosamprenavir calcium 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.

nossible resistance to Fosamprenavir

calcium or to the class of protease

Fosamprenavir calcium /ritonavir:

Use of lurasidone is contraindicated due to

potential for serious and/or life-threatening

Discontinue use of bosentan at least 36

hours prior to initiation of fosamprenavir

Maximum daily dose of 0.6 mg (may be

Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day). A complete blood count should be Rifabutin and rifabutin performed weekly and as clinically indicated metabolite to monitor for neutropenia Fosamprenavir calcium A dosage reduction of rifabutin by at least half the recommended dose is required. Fosamprenavir calcium/ritonavir: Dosage reduction of rifabutin by at least 75% of the usual doce of recommended (a maximum dose of 150 mg every other day or 3 times per week) Coadministration is contraindicated as it ↓Amprenavi

Treatment of FMF:

inhibitors [see Contraindications (4)]. Fosamprenavir calcium or fosamprenavi Antineoplastics: Dasatinib, ↑Antineoplastics concentrations of antineoplastics vinblastine, everolimus metabolized by CYP3A, potentially increasing the risk of adverse events typically associated with these medications In case of coadministration, please refer to relevant prescribing information for these medications. Antipsychotic Fosamprenavir calcium: If coadministration is necessary, reduce the Lurasidone †Lurasidone lurasidone dose. Refer to the lurasidone prescribing information for concomitant use with moderate CYP3A4 inhibitors

reactions [see Contraindications (4)]. Coadministration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias [see Contraindications (4)] Quetiapine ↑Quetiapine Fosamprenavir calcium /ritonavir: Initiation of fosamprenavir calcium with itonavir in patients taking quetiapine Consider alternative antiretroviral therapy t avoid increases in quetiapine drug exposures. If coadministration is necessar reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiaping associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction

monitorina. Initiation of quetiapine in patients taking fosamprenavir calcium with ritonavir: Refer for initial dosing and titration of quetiapine ↑ Benzodiazepines Clinical significance is unknown. A decrease n benzodiazepine dose may be needed.

Use with caution. Clinical monitoring of Calcium channel blockers: ↑ Calcium channel blockers Diltiazem, felodipine patients is recommended. nifedipine, nicardipin nimodipine, verapamil amlodipine, nisoldipine isradipine Use with caution. Fosamprenavir calcium Corticosteroid Dexamethasone may be less effective due to decreased amprenavir plasma concentrations. Endothelin-receptor ↑ Bosentan Coadministration of bosentan in patients on antagonist fosamprenavir calcium: In patients who have been receiving fosamprenavir calcium for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability Coadministration of fosamprenavir calcium in patients on bosentan:

After at least 10 days following the initiation of fosamprenavir calciur resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Ergot derivatives ↑Ergot derivatives Coadministration is contraindicated due to Dihydroergotamine potential for serious and/or life-threatening ergonovine, ergotamine, reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues [see Contraindications (4)]. Coadministration is contraindicated due to GI motility agent: †Cisapride potential for serious and/or life-threatening reactions such as cardiac arrhythmias [see

ontraindications (4)] Coadministration is contraindicated as it Herbal product ↓Amprenavi St. John's wort may lead to loss of virologic response and (Hypericum perforatum possible resistance to Fosamprenavir calcium or to the class of protease inhibitors [see Contraindications (4)] Histamine H2-receptor Fosamprenavir calcium Use with caution. Fosamprenavir calcium ↓ Amprenavir may be less effective due to decreased Cimetidine, famotidine amprenavir plasma concentrations. Fosamprenavi nizatidine, ranitidine<sup>a</sup> calcium/ritonavir Interaction not evaluated munosuppressants:

Therapeutic concentration monitoring is recommended for immunosuppressant Cyclosporine, tacrolimus, Inhaled beta-agonist: Concurrent administration of salmeterol with fosamprenavir calcium 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: Use with caution. Consider alternatives to Fosamprenavir calcium fluticasone, particularly for long-term use. Fosamprenavir May result in significantly reduced serum calcium/ritonavii cortisol concentrations. Systemic ↑ Fluticasone 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 fosamprenavir calcium/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects

†Atorvastati Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed atorvastatin 20 mg/da ↑Lovastatin Lovastatin, simvastatir . †Simvastatir Coadministration with lovastatin or simvastatin is contraindicated due to potential for serious reactions such as risk Other lipid modifying of myopathy including rhabdomyolysis [see agents: †Lomitapide Coadministration with lomitapide is contraindicated due to potential for markedly increased transaminases Narcotic analgesic: I Methadone Data suggest that the interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms. ↑Fentanyl Careful monitoring of therapeutic effects

notentially fatal respiratory depression) is recommended. Oral contraceptives Alternative methods of non-hormonal contracention are recommended May lead to loss of virologic response.<sup>a</sup> Fosamprenavir calcium Increased risk of transaminase elevations. Fosamprenavir calcium/ritonavir No data are available on the use of fosamprenavir calcium/ritonavir with other Ethinyl estradiol hormonal therapies, such as hormone replacement therapy (HRT) for

and adverse effects of fentanyl (including

postmenopausal women

PATIENT INFORMATION **FOSAMPRENAVIR** (foss-am-PREN-ah-ver) **CALCIUM TABLETS** Rx only

What is the most important information I should know about fosamprenavir calcium

Fosamprenavir calcium tablets can interact with other medicines and cause serious side effects. It is important to know the medicines that should not be taken with fosamprenavir calcium tablets. See the section "Who should not take fosamprenavir calcium tablets?" fosamprenavir calcium tablets can cause serious side effects, including:

· Severe skin reactions. fosamprenavir calcium tablets may cause severe or lifethreatening skin reactions or rash. If you get a rash with any of the following symptoms, stop taking fosamprenavir calcium tablets and call your healthcare

provider or get medical help right away: o hives or sores in swelling of your your mouth, or face, eyes, lips, your skin or blisters tongue, throat and peels

o trouble swallowing or breathing

For more information about side effects, see "What are the possible side effects of fosamprenavir calcium tablets?" What are fosamprenavir calcium tablets?

Fosamprenavir calcium tablets are prescription medicines that are used together with other antiretroviral medicines to treat human immunodeficiency virus 1 (HIV-1) infection.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS). It is not known if fosamprenavir calcium

tablets are safe and effective in children younger than 4 weeks of age. Do not take fosamprenavir calcium tablets if

 are allergic to amprenavir, fosamprenavir calcium, or any of the ingredients in fosamprenavir calcium tablets. See the end of this leaflet for a complete list of ingredients in fosamprenavir calcium

take any of the following medicines:

 alfuzosin o rifampin

o ergot including:

dihydroergotamine mesylate ergonovine

ergotamine tartrate methylergonovine

cisapride St. John's wort (Hypericum perforatum)

 lomitapide lovastatin o simvastatin

pimozide o delavirdine mesylate o sildenafil (REVATIO), for treatment of

pulmonary arterial hypertension

 triazolam midazolam, when taken by mouth Serious problems can happen if you or your

child take any of the medicines listed above with fosamprenavir calcium tablets. If you are taking fosamprenavir calcium

tablets with ritonavir, do not take the following medicines:

 flecainide propafenone

> lurasidone Before taking fosamprenavir calcium

> tablets, tell your healthcare provider about all of your medical conditions, including if · are allergic to medicines that contain sulfa.

> · have or have had liver problems, including hepatitis B or C virus infection.

have kidney problems.

 have high blood sugar (diabetes). have hemophilia. have high cholesterol.

 are pregnant or plan to become pregnant. It is not known if fosamprenavir calcium tablets will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant during treatment with fosamprenavir calcium tablets.

o fosamprenavir calcium tablets may reduce

how well hormonal contraceptives (birth

control pills) work. Females who may

become pregnant should use a different form of birth control or an additional barrier method of birth control during treatment with fosamprenavir calcium tablets. **Pregnancy Registry.** There is a pregnancy registry for women who take fosamprenavir calcium tablets during pregnancy. The purpose of the registry is to collect

how you can take part in this registry. are breastfeeding or plan to breastfeed. Do not breastfeed if you take fosamprenavir calcium tablets.

information about the health of you and your

baby. Talk to your healthcare provider about

 You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to o It is not known if fosamprenavir calcium tablets can pass to your baby in your breast

 $\circ$  Talk with your healthcare provider about the best way to feed your baby. Tell your healthcare provider about all the medicines you take, including prescription

Keep a list of your medicines to show your healthcare provider and pharmacist. You can ask your healthcare provider or pharmacist for a list of medicines that

and over-the-counter medicines, vitamins,

and herbal supplements. Some medicines

interact with fosamprenavir calcium tablets.

interact with fosamprenavir calcium tablets. Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take fosamprenavir calcium tablets with other medicines.

tablets? Take fosamprenavir calcium tablets exactly as your healthcare provider tells you to take it.

If you miss a dose of fosamprenavir

How should I take fosamprenavir calcium

calcium tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than your healthcare provider tells you to take. · Stay under the care of a healthcare provider

during treatment with fosamprenavir calcium tablets. If your child is taking fosamprenavir calcium tablets, your child's healthcare provider will decide the right dose based on

your child's weight. fosamprenavir calcium tablets tablets may be taken with or without food.

 Do not run out of fosamprenavir calcium tablets. The virus in your blood may

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increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.

· If you take too much fosamprenavir calcium tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of fosamprenavir calcium tablets? Fosamprenavir calcium tablets may cause

serious side effects including: See "What is the most important information I should know about fosamprenavir calcium tablets?"

· Liver problems. Your healthcare provider should do blood tests before and during your treatment with fosamprenavir calcium tablets to check your liver function. Some people with liver problems, including hepatitis B or C, may have an increased risk of developing worsening liver problems during treatment with fosamprenavir

calcium tablets. Diabetes and high blood sugar (hyperglycemia). Some people who take inhibitors, including fosamprenavir calcium tablets, can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often during treatment with fosamprenavir calcium tablets.

 Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.

 Increase in body fat. An increase in body fat can happen in people who take protease inhibitors, including fosamprenavir calcium tablets. The exact cause and long-term health effects of these conditions are not

 Changes in blood tests. Some people have changes in blood tests while taking fosamprenavir calcium tablets. These include an increase in liver function tests, blood fat levels (cholesterol and triglycerides) and decrease in red blood cells. Your healthcare provider should do regular blood tests before and during your treatment with fosamprenavir calcium

 Increased bleeding problems in some people with hemophilia. Some people with hemophilia have increased bleeding with protease inhibitors, including fosamprenavir calcium tablets.

• Kidney stones. Some people have developed kidney stones during treatment with fosamprenavir calcium tablets. Tell your healthcare provider right away if you develop any of the following signs or symptoms of kidney stones:

o pain in your side

blood in your urine

o pain when you urinate The most common side effects of fosamprenavir calcium tablets in adults

include: nausea diarrhea headache

 vomiting rash

The most common side effects of fosamprenavir calcium tablets in children include vomiting and decrease in white blood

These are not all the possible side effects of fosamprenavir calcium tablets.

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

How should I store fosamprenavir calcium tablets?

 Store fosamprenavir calcium tablets at room temperature between 68° F to 77° F

(20° C to 25° C). · Keep the bottle of fosamprenavir calcium

tablets tightly closed. Protect from moisture.

Keep fosamprenavir calcium tablets and all medicines out of the reach of children.

General information about the safe and effective use of fosamprenavir calcium tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use fosamprenavir calcium tablets for a condition for which it was not prescribed. Do not give fosamprenavir calcium tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about fosamprenavir calcium

tablets that is written for health professionals. What are the ingredients in fosamprenavir calcium tablets? Active ingredient: fosamprenavir calcium

(amorphous). **Inactive ingredients:** colloidal silicon dioxide. croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone. The tablet coating contains the inactive ingredients ethylcellulose, ferric oxide red, hypromellose, talc, and titanium dioxide. The imprinting ink contains the inactive ingredients ferric oxide black, propylene glycol, and shellac.

This Patient Information has been approved by the U.S. Food and Drug Administration. The brands listed are trademarks of their respective owners.

Manufactured by: Ohm Laboratories Inc. New Brunswick, NJ 08901 Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512

May 2019 FDA-05

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
PDE5 inhibitors: Sildenafil, tadalafil, vardenafil	† Sildenafii † Tadalafii † Vardenafii	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 sildenafii (REVATIO) is contraindicated when used for the treatment of PAH. A safe and effective dose has not been established when used with fosamprenavir calcium. There is increased potential for sildenafii-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope) (see Contraindications (4)).  The following dose adjustments are recommended for use of tadalafii (ADCIRCA®) with fosamprenavir calcium:  Coadministration of ADCIRCA in patients on fosamprenavir calcium: In patients receiving fosamprenavir calcium for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.  Coadministration of fosamprenavir calcium. Stop ADCIRCA at least 24 hours prior to starting fosamprenavir calcium. After at least one week following the initiation of fosamprenavir calcium. Stop ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.  Use of PDE5 inhibitors for erectile dysfunction: Fosamprenavir calcium: Sildenafii: 25 mg every 48 hours. Tadalafi: no more than 10 mg every 72 hours. Vardenafii: no more than 2.5 mg every 24 hours. Tadalafi: no more than 1.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours. Vardenafii: no more than 2.5 mg every 72 hours.
Proton pump inhibitors: Esomeprazole <sup>a</sup> , lansoprazole, omeprazole, pantoprazole, rabeprazole	Fosamprenavir calcium:  → Amprenavir  ↑ Esomeprazole Fosamprenavir calcium/ritonavir:  → Amprenavir  → Esomeprazole	Proton pump inhibitors can be administered at the same time as a dose of fosamprenavir calcium with no change in plasma amprenavir concentrations.
Sedative/hypnotics: Midazolam, triazolam	↑Midazolam ↑Triazolam	Coadministration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression [see Contraindications (4)].
Tricyclic antidepressants:	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants.

Amitriptyline, imipramine <sup>a</sup> See Clinical Pharmacology (12.3) Tables 10, 11, 12, or 13 for magnitude of interaction

8 USE IN SPECIFIC POPULATIONS

readucate provides are encouraged to register patients by dailing the intineutownal registrating registry (km y at 1-600-220-4205. Risk Summary Limited data are available for use of fosamprenavir calcium in pregnancy, fosamprenavir calcium 700 mg twice daily should only be considered in pregnant patients who are already on a stable twice-daily regimen of fosamprenavir calcium/infoam/700 mg/100 mg prior to pregnancy, and who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) (see Clinical Considerations and Data).

Clinical Considerations and Data). There are insufficient human data on the use of fosamprenavir during pregnancy to adequately assess a drug-associated risk for birth defects and miscarriage. Given the limited number of pregnancies exposed to fosamprenavir-based regimens, no conclusions can be drawn on the safety of fosamprenavir in pregnancy. The background risk for major birth defects and miscarriage for the indicated population is unknown. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Formation print defects in a U.S. reference population of the Metropolitan Atlanta Formation and the proposition of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in a U.S. reference population of the Metropolitan Atlanta for major birth defects in general population is 1376 to 2076. 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 as the inaximum recommenues human dose (MRHD) with or without intonavir. 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 postnatal 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 off opamprenavir alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir in combination with ritionavir (see Data).

Clinical Considerations

Virologic Monitoring During Pregnancy and the Postpartum Period: Based on limited data on the use of fosamprenavir calcium during

Virologic Monitoring During Pregnancy and the Postpartum Period: Based on limited data on the use of fosamprenavir calcium during pregnancy, no dosage adjustments are required for pregnant patients who are already on a stable twice-daily regimen of fosamprenavir calcium 700 mg taken with ritonavir 100 mg prior to pregnancy, and who are virologically suppressed (HIV-1 HINA less than 50 copies m L) (see Dosage and Administration (2.3), Clinical Pharmacology (12.3). In a clinical trial of 10 HIV-1-infected pregnant women treated with tosamprenavir calcium 700 mg taken with ritonavir 100 mg twice daily through postpartum, total amprenavir exposures were lower during pregnancy compared with the postpartum period. Therefore, viral load should be monitored closely to ensure viral suppression is maintained [see Data, Dosage and Administration (2.2), Clinical Pharmacology (12.3)]. Pregnancy data with other dosage regimens of fosamprenavir calcium (with or without ritonavir) are not available.

Data
Human Data: fosamprenavir calcium 700 mg taken with ritonavir 100 mg twice daily in combination with a background regimen was evaluated in a clinical trial of 10 HIV1-infected pregnant women during the second and third trimesters and postpartum. Subjects initiated fosamprenavir calcium /ritonavir during pregnancy at a median of 19 weeks' gestation; 4 had undetectable HIV-1 RINA viral load (less than 50 copies/mil.) at the time of initiation. Amprenavir pharmacokinetics and placental transfer were studied during the second trimester (= 6) or third trimester (n = 9) and postpartum (n = 9). Pregnancy outcomes were available for all 10 subjects, among which 1 twin pregnancy was included. Compared to the postpartum period, geometric mean maprenavir ALD was 35% lower in the third trimester. The amprenavir geometric mean ratio (95% CI) of fetal cord to maternal peripheral plasma concentration (n = 7) was 0.27 (0.24 to 0.30) (see Clinical Pharmacology (7.23)). At delivery, 9 subjects had HIV-1 tola delass than 50 copies/mil. and 1 subject had a viral load of 111 copies/mil. All 11 infants born had test results that were negative for HIV-1 at the time of reliaives and through 12 months pencharum. These were no new cafets findings compared with the known scales for fiscomprenaries of resomprenaries. of delivery and through 12 months postpartum. There were no new safety findings compared with the known safety profile of fosamp calcium /ritonavir in HIV-1-infected adults.

action /monavir in rive-i-infected addits. Based on prospective reports to the APR of approximately 146 live births following exposure to fosamprenavir-containing regimens, there Based on prospective reports to the APH of approximately 146 live births following exposure to tosamprenain-containing regimens, there were 2 birth defects reported in 109 first trimester exposures. The background rate for major birth defects is 2.7% in a U.S. reterence population of the MACDP. Prospective reports from the APR of overall major birth defects in pregnancies exposured to fosamprenaivir are compared with the U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations as well as conflounding due to the underlying disease. Animal Data: Fosamprenaivir was administered orally to prepanal rats (300, 820, or 2.240 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 obspaned of these does beloed, resulting in exercise (3.00). Approximately climine (1.00) and 8 times (rabbist) human exposures. 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-retail development were observed at these dose levels, resulting in exposures (AUC<sub>P24h</sub>) 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 samprenavir in combination with ritinavir. However, increased incidence of abortion was observed in rabbits administered a maternally toxic dose of fosamprenavir (fo? 8 mg per kg per day). In a study where amprenavir was administered orally tox repeant rabbits (2.5, 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 fermir, humerus, and trochlea) were observed at doses that produced approximately one-twentieth the exposure seen at the MRHD. In the rat pre- and postnatal development study, fosamprenavir was administered orally (300, 802, or 2.240 mg per kg per day) on Gestation Day 6 to Lactation/Postpartum Day 20. Fosamprenavir caused a reduction in pup survival and body weights. In surviving female offspring from the high-dose group, an increased efficient possition, and an increased engine of gestation, a reduction unber of uterine implantation sites per litter, and reduced gestational body weights were observed. Systemic exposure (AUC<sub>Q-34-3</sub>) 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 alone or approximately the same as those seen in humans at the MRHD of fosamprenavir in combination with ritonavir.

8.2 Lactation

Risk Summary
The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants The Centers for Disease Control and Prevention recommends that HIV-1-intected mothers in the unined states flow ureasured unint intection.

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 lacating 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) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving fosamprenavir calcium.

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 Polential Contraception
Use of losamprenavir calcium 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

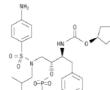
8.4 Pediatric Use The safety, pharmacokinetic profile, and virologic and immunologic responses of fosamprenavir calcium with and without ritonavir were evaluated in protease inhibitor-naive and -experienced HIV-1-infected pediatric subjects aged at least 4 weeks to younger than 18 years and weighing at least 3 kg in 3 open-label trials [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]. Treatment with fosamprenavir calcium is not recommended in protease inhibitor-experienced pediatric patients younger than 6 months. The pharmacokinetics, safety, tolerability, and efficacy of fosamprenavir calcium in pediatric patients younger than 4 weeks have not bestablished (see Clinical Pharmacology (12.3)). Available pharmacokinetic and clinical data do not support once-daily dosing of fosamprenavir calcium alone or in combination with ritonavir for any pediatrics or twice-daily dosing without ritonavir in pediatric patients

ounger than 2 years (*see Clinical Pharmacology (12.3), Clinica*l Studies (14.3)]. See Dosage and Administration (2.3) for dosing scommendations for pediatric patients. 8.5 Geriatric Use to definite use the samprenavir calcium 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. 8.6 Hepatic Impairment
Amprenavir is principally metabolized by the liver; therefore, caution should be exercised when administering fosampre

patients with hepatic impairment because amprenavir concentrations may be increased [see Clinical Pharmacology (12.3)]. Patients with impaired hepatic function receiving fosamprenavir calcium with or without concurrent ritonavir require dose reduction [see Dosage and nere are no data to support dosing recommendations for pediatric subjects with hepatic impairment. 10 OVERDOSAGE

In a healthy volunteer repeat-dose pharmacokinetic trial evaluating high-dose combinations of fosamprenavir calcium plus ritonavir, an increased frequency of Grade 29 ALT elevations (greater than 2.5 x U.L.N) was observed with fosamprenavir calcium 1,400 mg twice daily plus ritonaviz 200 mg twice daily (4 of 25 subjects). Concurrent Grade 1/2 elevations in AST (greater than 1.25 x U.L.N) were noted in 3 of these 4 subjects. These transaminase elevations resolved following discontinuation of dosing. There is no known antidote for fosamprenavir calcium. 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.

Fosamprenavir calcium is a prodrug of amprenavir, an inhibitor of HIV protease. The chemical name of fosamprenavir calcium is (3S)-tetrahydrofuran-3-yl (152R)-3-[[(4-aminophenyl) sulfonyl)[(sobutyl)amino)-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3S)(15.2R) configuration. It has a molecular veright of C2.1/L it has the following structural formula:



osamprenavir calcium (amorphous) is a white to cream color powder which is soluble in methanol Fosamprenavir calcium tablets are available for oral administration in a strength of 70 m g of fosamprenavir as fosamprenavir calcium (amorphous) (equivalent to approximately 600 mg of amprenavir). Each 700 mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone. The tablet coating contains the inactive ingredients thriftlycellulose, froir oxide red, hypormellose, talc, and titanium dioxide. The imprinting ink contains the inactive ingredients ferric oxide black, propylene glycol, and shellac.

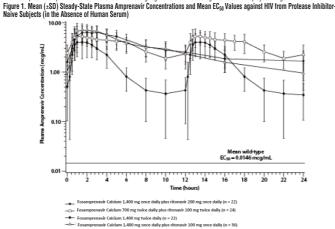
12 CLINICAL PHARMACOLOGY imprenavir is an HIV-1 antiretroviral agent [see Microbiology (12.4)].

The pharmacokinetic properties of amprenavir after administration of fosamprenavir calcium, 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 fosamprenavir calcium (with and without concomitant ritonavir) are shown in Table 7.

able 7. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters in Adults								
Regimen	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> (hours) <sup>a</sup>	AUC24 (mcg•h/mL)	Ctau b (mcg/mL)				
Fosamprenavir calcium 1,400 mg Twice Daily (n = 22) <sup>c</sup>	4.82 (4.06 to 5.72)	1.3 (0.8 to 4)	33 <sup>d</sup> (27.6 to 39.2)	0.35 (0.27 to 0.46)				
Fosamprenavir calcium 1,400 mg Once Daily plus Ritonavir 200 mg Once Daily (n = 22)°	7.24 (6.32 to 8.28)	2.1 (0.8 to 5)	69.4 (59.7 to 80.8)	1.45 (1.16 to 1.81)				
Fosamprenavir calcium 1,400 mg Once Daily plus Ritonavir 100 mg Once Daily (n = 36) <sup>e</sup>	7.93 (7.25 to 8.68)	1.5 (0.75 to 5)	66.4 (61.1 to 72.1)	0.86 (0.74 to 1.01)				
Fosamprenavir calcium 700 mg Twice Daily plus Ritonavir 100 mg Twice Daily (n = 24)°	6.08 (5.38 to 6.86)	1.5 (0.75 to 5)	79.2 <sup>d</sup> (69 to 90.6)	2.12 (1.77 to 2.54)				

<sup>1</sup> Data shown are median (range). <sup>0</sup> C<sub>tau</sub> is the concentration at the end of the dose interval.  $^d$  AUC $_{\!24}$  was calculated from AUC $_{\!12}$  summary data x 2.  $^e$  Healthy adults.

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



Absorption
After administration of a single dose of fosamprenavir calcium to HIV-1-infected subjects, the time to peak amprenavir concentration (T<sub>max</sub>) occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of fosamprenavir calcium in humans has not been established. fosamprenavir calcium in humans has not been established.
After administration of a single 1,400-mg dose in the fasted state, fosamprenavir calcium oral suspension (50 mg per mL) and fosamprenavir calcium tablets (700 mg) provided similar amprenavir exposures (AUC); however, the C<sub>max</sub> of amprenavir after administration of the suspension formulation was 14.5% higher companed with the tablet.
Amprenavir is both a substrate for and inducer of P-glycoprotein.

Administration of a single 1,400 mg dose of fosamprenavir calcium tablets in the fed state (standardized high-fat meal: 967 kcal, 67 grams tat, 33 grams protein, 58 grams carbohydrate) compared with the fasted state was associated with no significant changes in amprenavir C<sub>max</sub>, T<sub>max</sub>, or AUC<sub>0-m</sub> (see Dosage and Administration (2)). Administration of a single 1,400 mg dose of fosamprenavir calcium or all 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<sub>max</sub>, a 0.72-hour delay in T<sub>max</sub>, and a 28% reduction in amprenavir AUC<sub>0-m</sub>.

Distribution

In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to alpha-racid 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. Nettabolism
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 anilline 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 \*\*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.

Specific Populations
Patients with Hepatic Impairment: The pharmacokinetics of amprenavir have been studied after the administration of fosamprenavi

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The pharmacokinetics of amprenavir have been studied after the administration of fosamprenavir have been stu radients with repeate impariment. In plantations of a plantation with a consistent may be determined and severe hepatic impariment. Following 2 weeks of dosing with fosamprenavir calcium 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 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 (2.4)l.

The pharmacokinetics of amprenavir have been studied after administration of amprenavir given as AGENERASE® 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 approximately 23 vibral modeless are indealing and a second manager of the indealing volunteers (see Dosage and Administration (2.4)). 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.

Pregnant Womer: Amprenavir pharmacokinetics were studied in pregnant women receiving fosamprenavir calcium (700 mg) plus ritonavir (100 mg) twice daily during the second trimester (n = 6) or third trimester (n = 9) and postpartum (n = 9). Compared to postpartum, geometric mean amprenavir AUC was 35% lower in the second trimester and 25% lower in the third trimester [Table 8]. This decrease results in amprenavir concentrations that are within the range observed across regimens of fosamprenavir calcium in non-pregnant adult and over concentrations compared with fosamprenavir calcium (700 mg) plus ritoravir (100 mg) withe dayl in non-pregnant adult (71 mg). This decrease is not expected to be considered clinically relevant in patients who are virologically supersesed, however vital load should be monitored closely to ensure vital suppression is maintained (see Dosage and Administration (2.2). Use in Specifi Populations (8.1). The amprenavir geometric mean ratio (95% CI) of fetal cord to maternal peripheral plasma concentration (n = 7) wa 0.27 (0.24 to 0.50).

Pharmacokinetic	Fosamprenavir calcium 70	00 mg Twice Daily plus Rito	navir 100 mg Twice	
Parameter	Second Trimester	Third Trimester	Postpartum	
	(n = 6)	(n = 9)	(n = 9)	
UC <sub>12</sub> (mcg•h/mL)	26.0	30.1	39.9	
	(19.5, 34.6)	(21.6, 41.9)	(31.9, 50.1)	
IC <sub>24</sub> (mcg•h/mL) <sup>a</sup>	52.0	60.2	79.8	
	(39.0, 69.2)	(43.2, 83.8)	(63.8, 100.2)	
C <sub>max</sub> (mcg/mL)	4.19	5.36	6.65	
	(3.19, 5.51)	(3.98, 7.22)	(5.24, 8.44)	
Ctau (mcg/mL) <sup>b</sup>	1.31	1.34	2.03	
	(0.97, 1.77)	(0.95, 1.89)	(1.46, 2.83)	

Pediatric Patients: The pharmacokinetics of amprenavir following administration of fosamprenavir calcium oral suspension and fosamprenavir calcium tablets, with or without ritonavir, have been studied in a total of 212 HIV-1-infected pediatric subjects enrolled in 3 trials. Fosamprenavir calcium without ritonavir was administered as 30 or 40 mg per kg twice daily to children aged 2 to 5 years Fosamprenavir calcium with ritonavir was administered as fosamprenavir calcium 30 mg per kg plus ritonavir 6 mg per kg once daily to children aged 2 to 18 years and as fosamprenavir calcium 18 to 60 mg per kg plus ritonavir 3 to 10 mg per kg twice daily to children ager at least 4 weeks to 18 years, body weights ranged from 3 to 103 xg. Amnrenavir annarent clearance decreased with increasing weight. Weight-adjusted apparent clearance was higher in children younger than Amprenavir apparent clearance decreased with increasing weight. Weight-adjusted apparent clearance was higher in children younger than 4 years, suggesting that younger children require higher mg-per-kg dosing of fosamprenavir calcium.

The pharmacokinetics of fosamprenavir calcium oral suspension in protease inhibitor-naive infants younger than 6 months (n = 9) receiving fosamprenavir calcium 45 mg per kg plus ritonavir 10 mg per kg huise daily generally demonstrated lower AUC12 and C<sub>mis</sub> than adults receiving twice-daily fosamprenavir calcium 70 mg plus ritonavir 100 mg, the dose recommended for protease-sevenced adults. The mean steady-state amprenavir AUC12, C<sub>mis</sub>, and C<sub>mis</sub> were 26.6 mcp-hour per mL, 6.25 mcg per mL, and 0.86 mcg per mL, respectively. Because of expected low amprenavir exposure and a requirement for large volume of drug, twice-daily dosing of fosamprenavir calcium alone (without ritonavir) in pediatric subjects younger than 2 years was not studied.

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

<sup>b</sup> C<sub>tau</sub> represents the concentration at the end of the dose interval

Weight	Recommended		Cmax	iving Fosamprenavir Calcium with Riton AUC24		Cmin	
g	Dosage Regimen	l Adda				· · · · · · · · · · · · · · · · · · ·	
		n	(mcg/mL)	n	(mcg•h/mL)	n	(mcg/mL)
< 11 kg	Fosamprenavir	12	6 (3.88, 9.29)	12	57.3	27	1.65
	calcium 45 mg/kg plus Ritonavir 7 mg/kg twice daily				(34.1, 96.2)		(1.22, 2.24)
1 kg - < 15 kg	Fosamprenavir calcium 30 mg/kg plus Ritonavir 3 mg/kg twice daily	Not studied <sup>a</sup>					
5 kg - < 20 kg	Fosamprenavir calcium 23 mg/kg plus Ritonavir 3 mg/kg twice daily	5	9.54 (4.63, 19.7)	5	121 (54.2, 269)	9	3.56 (2.33, 5.43)
0 kg - < 39	Fosamprenavir	13	6.24	12	97.9	23	2.54
kg	calcium 18 mg/kg plus Ritonavir 3 mg/kg twice daily		(5.01, 7.77)		(77, 124)		(2.11, 3.06)
≥ 39 kg	Fosamprenavir	15	5.03	15	72.3	42	1.98
	calcium 700 mg plus Ritonavir 100 mg twice daily		(4.04, 6.26)		(59.6, 87.6)		(1.72, 2.29)

mg twice daily

Recommended dose for pediatric patients weighing 11 kg to less than 15 kg is based on population pharmacokinetic analysis.

Subjects aged 2 to younger than 6 years receiving fosamprenavir calcium 30 mg per kg twice daily without ritonavir achieved geometric mean (95% CI) amprenavir C<sub>max</sub> (n = 9), AUC<sub>12</sub> (n = 9), and C<sub>min</sub> (n = 19) of 7.15 (5.05, 10.1), 22.3 (15.3, 32.6), and 0.513 (0.384, 0.686) considerations. The pharmacokinetics of amprenavir after administration of fosamprenavir calcium to patients older than 65 years have not been studied [see Use in Specific Populations (8.5)]. Male and Female Patients: The pharmacokinetics of amprenavir after administration of fosamprenavir calcium do not differ between males

Racial Groups: The pharmacokinetics of amprenavir after administration of fosamprenavir calcium do not differ between blacks and non-blacks [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. Amprenavii 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 no nhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or undine glucuronosyltransferase (UDPGT). Amprenavir is both a substrate for

and inducer or P-group rotein.

Drug interaction trials were performed with fosamprenavir calcium and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration on AUC, C<sub>max</sub>, and C<sub>min</sub> values are summarized in Table 10 (effect of other drugs on amprenavir) and Table 12 (effect of fosamprenavir calcium on other drugs). In addition, since fosamprenavir calcium delivers comprante amprenavir plasma concentrations as AGENERASE (rug interaction data derived from trials with AGENERASE are provided in Tables 11 and 13. For information regarding clinical recommendations, (see Drug Interactions (7)). Table 10. Drug Interactions: Pharmacokinetic Parameters for Amprenavir after Administration of Fosampre

Coadministered Drun(s) Dose of Fosamorenavir

Coadministered Drug(s)	Dose of Fosamprenavir		Parameters (90% CI		
and Dose(s)	Calcium <sup>a</sup>	n	Cmax	AUC	Cmin
Antacid (MAALOX TC)	1,400-mg	30	↓ 35	↓ 18	↑ 14
30 mL single dose	single dose	-00	(↓ 24 to ↓ 42)	(↓ 9 to ↓ 26)	(↓ 7 to ↑ 39)
Atazanavir 300 mg once daily for	700 mg twice daily plus ritonavir 100 mg twice daily	22	↔	↔	↔
10 days	for 10 days				
Atorvastatin	1,400 mg twice daily for 2	16	. 10	↓ 27	⊥ 12
10 mg once daily for	weeks		↓ 18 (↓ 34 to ↑ 1)	(↓ 41 to ↓	( 27 to 16)
4 days			(‡ 04 10   1)	12)	(1 27 10 1 0)
Atorvastatin 10 mg once daily for	700 mg twice daily plus ritonavir 100 mg twice daily	16	↔	↔	↔
4 days	for 2 weeks				
Efavirenz	1,400 mg once daily plus	16		. 10	. 20
600 mg once daily for	ritonavir 200 mg once daily		↔	↓ 13 (↓ 30 to ↑ 7)	↓ 36 (↓ 8 to ↓ 56)
2 weeks	for 2 weeks	40		(1001017)	(1 0 10 1 00)
Efavirenz 600 mg once daily plus	1,400 mg once daily plus ritonavir 200 mg once daily	16			
additional ritonavir	for 2 weeks		↑ 18	↑11 (0.1 1.0 0.0	↔
100 mg once daily for			(↑ 1 to ↑ 38)	(0 to ↑ 24)	
2 weeks					
Efavirenz	700 mg twice daily plus ritonavir 100 mg twice daily	16			↓ 17
600 mg once daily for 2 weeks	for 2 weeks		↔	↔	(↓ 4 to ↓ 29)
Esomeprazole	1,400 mg twice daily for 2	25			
20 mg once daily for	weeks		↔	↔	↔
2 weeks					
Esomeprazole 20 mg once daily for	700 mg twice daily plus ritonavir 100 mg twice daily	23			↔
2 weeks	for 2 weeks				
Ethinyl	700 mg twice daily plus	25			
estradiol/norethindrone	ritonavir <sup>b</sup> 100 mg twice		↔°	↔°	↔°
0.035 mg/0.5 mg once daily for 21 days	daily for 21 days				
Ketoconazole <sup>d</sup>	700 mg twice daily plus	15			
200 mg once daily for	ritonavir 100 mg twice daily		↔	↔	↔
4 days	for 4 days				
Lopinavir/ritonavir	1,400 mg twice daily for 2	18	. 408	. 00*	. 400
533 mg/133 mg twice daily	weeks		↓ 13°	↓ 26e	↓ 42 <sup>e</sup>
Lopinavir/ritonavir	700 mg twice daily plus	18		⊥ 63	⊥ 65
400 mg/100 mg twice	ritonavir 100 mg twice daily		↓ 58 (⊥ 42 to ⊥ 70)	(↓ 51 to ↓	(↓ 54 to ↓
daily for 2 weeks	for 2 weeks		(1 42 10 1 70)	72)	73)
Maraviroc 300 mg twice daily for	700 mg twice daily plus ritonavir	14	↓34	↓ 35 (↓ 29 to ↓	↓ 36
10 days	100 mg twice daily for		(↓ 25 to ↓41)	41)	(↓ 27 to ↓
-	20 days				43)
Maraviroc	1,400 mg once daily	14	↓ 29	↓30	. 15
300 mg twice daily for 10 days	plus ritonavir 100 mg once daily for		(↓ 20 to ↓38)	(↓23 to ↓36)	↓ 15 (↓3 to ↓25)
	20 days				(+= == +==)
Methadone	700 mg twice daily plus	19	_		
70 to 120 mg twice	ritonavir 100 mg twice daily		↔°	↔°	↔°
daily for 2 weeks Nevirapine	for 2 weeks 1,400 mg twice daily for 2	17		↓ 33	↓ 35
200 mg twice daily for	weeks	''	↓ 25 (	(↓ 45 to ↓	(↓ 50 to ↓
2 weeks <sup>1</sup>			(↓ 37 to ↓ 10)	20)	15)
Nevirapine	700 mg twice daily plus	17		↓ 11	↓ 19
200 mg twice daily. for 2 weeks <sup>1</sup>	ritonavir 100 mg twice daily for 2 weeks		↔	(↓ 23 to ↑ 3)	(↓ 32 to ↓ 4)
Phenytoin	700 mg twice daily plus	13		4.00	4.10
300 mg once daily for	ritonavir 100 mg twice daily		↔	↑ 20 (↑ 8 to ↑ 34)	↑ 19 (↑ 6 to ↑ 33)
10 days	for 10 days				
Raltegravir 400 mg twice daily for	1,400 mg twice daily for 14 days (fasted)	14	↓ 27	↓ 36 (↓ 53 to ↓	↓ 43° (↓ 59 to ↓
14 days	days (lastou)		(↓ 46 to ↔)	13)	21)
	1,400 mg twice daily for 14	14	↓ 15	↓ 17	↓ 32 <sup>9</sup>
	days <sup>n</sup>	14	(↓ 27 to ↓ 1)	(↓ 27 to ↓ 6)	(↓ 53 to ↓ 1)
	700 mg twice daily plus ritonavir 100 mg twice daily	14	↓14	↓ 17 (↓ 38 to ↑	↓ 20° (↓ 45 to ↑
	for 14 days (fasted)		(↓ 39 to ↑ 20)	12)	17)
	700 mg twice daily plus	12	↓ 25	↓ 25	↓ 339
	ritonavir 100 mg twice daily		(↓ 42 to ↓ 2)	(↓ 44 to ↔)	(↓ 52 to ↓ 7)
Raltegravir	for 14 days <sup>h</sup> 1,400 mg once daily for14	13			↓ 50°
400 mg twice daily, for	days (fasted)		↓ 18 (⊥ 34 to ↔)	↓ 24 (⊥ 41 to ↔)	(↓ 64 to ↓
14 days			(↓ 34 10 ↔)	(↓ 41 t0 ↔)	31)
	1,400 mg once daily for 14	14	4.07	4.10	↓ 179
	days <sup>h</sup>		↑ 27 (↓ 1 to ↑ 62)	↑ 13 (↓ 7 to ↑ 38)	(↓ 45 to ↑
Ranitidine	1,400 mg single dose	30	(4 : 35   02)		26)
300 mg single dose	1,400 mg single dose	30	↓ 51	↓ 30	↔
(administered 1 hour			(↓ 43 to ↓ 58)	(↓ 22 to ↓ 37)	(↓ 19 to ↑ 21)
before fosamprenavir)					21)
Rifabutin 150 mg every other	700 mg twice daily plus ritonavir 100 mg twice daily	15	↑ 36°	↑ 35° (↑ 17 to ↑	↑ 17°
day for 2 weeks	for 2 weeks		(↑ 18 to ↑ 55)	56)	(↓ 1 to ↑ 39)
Tenofovir	700 mg twice daily plus	45	NA	NA NA	↔i
300 mg once daily for 4	ritonavir 100 mg twice daily				
to 48 weeks Tenofovir	for 4 to 48 weeks 1,400 mg once daily plus	60	NA	NA	↔i
300 mg once daily for 4	ritonavir 200 mg once daily	30			
to 48 weeks	for 4 to 48 weeks				

icomitant medication is also shown in this column where appropriate.

onavir C<sub>max</sub>, AUC, and C<sub>min</sub> increased by 63%, 45%, and 13%, respectively, compared with historical control.

Subjects were receiving fosamprenavir calcium/ritonavir for 10 days prior to the 4-day treatment period with both ketoconazole and fosamprena ared with fosamprenavir calcium 700 mg/ritonavir 100 mg twice daily for 2 weeks. ts were receiving nevirapine for at least 12 weeks prior to trial.

oses of fosamprenavir calcium and ralteoravir were given with food on pharmacokinetic sampling days and without regard to food all other days N = 18 for C<sub>min</sub>.

1 = 18 for C<sub>min</sub>.

1 = Increase; \( \perp \) = Decrease; \( \perp = \perp \) = No change († or \( \perp \) less than or equal to 10%), NA = Not applicable.

Coadministered Drug(s) and	Dose of	Paramete		% Change in Amprenavir Pharm Parameters Dose of (90% CI)		armacokinetio
Dose(s)	AGENERASE <sup>a</sup>	n	Cmax	AUC	Cmin	
Abacavir 300 mg twice daily for 2 to 3 weeks	900 mg twice daily for 2 to 3 weeks	4	↔ª	÷	⊖³	
Clarithromycin 500 mg twice daily for	1,200 mg twice daily for 4 days	12	↑ 15 (↑ 1 to ↑ 31)	↑ 18 (↑ 8 to ↑ 29)	↑ 39 (↑ 31 to ↑	

Abacavir	900 mg twice daily	4	↔3	↔3	↔²
300 mg twice daily for	for 2 to 3 weeks				
2 to 3 weeks					
Clarithromycin	1,200 mg twice daily	12	↑ 15	↑ 18	↑ 39
500 mg twice daily for	for 4 days		(↑ 1 to ↑ 31)	(↑ 8 to ↑ 29)	(↑ 31 to ↑ 47)
4 days					
Delavirdine	600 mg twice daily	9	↑ 40 <sup>b</sup>	↑ 130 <sup>b</sup>	↑ 125 <sup>b</sup>
600 mg twice daily for	for 10 days		· ·	· ·	
10 days					
Ethinyl	1,200 mg twice daily	10	<b>↔</b>	↓ 22	↓ 20
estradiol/norethindrone	for 28 days			( ↓ 35 to ↓ 8)	(↓ 41 to ↑ 8)
0.035 mg/1 mg for 1 cycle					
Indinavir	750 or 800 mg 3	9	↑18	↑ 33	↑ 25
800 mg 3 times a day for	times a day for 2		(† 13 to †	(↑ 2 to ↑ 73)	( 116) ( 27 to ↑ 116)
2 weeks (fasted)	weeks (fasted)		58)		
Ketoconazole	1,200-mg	12	↓16	↑ 31	NA
400-mg single dose	single dose		(  25 to   6)	(↑ 20 to ↑ 42)	
Lamivudine	600-mg	11	$\leftrightarrow$	$\leftrightarrow$	NA
150-mg single dose	single dose				
Methadone	1,200 mg mg once	16	↓ 27°	↓ 30°	↓ 25°
44 to 100 mg once daily	daily				
for	for 10 days				
> 30 days					
Nelfinavir	750 or 800 mg 3	6	↓14	$\leftrightarrow$	↑ 189
750 mg 3 times a day for	times a day for 2		(↓ 38 to ↑		(↑ 52 to ↑ 448)
2 weeks (fed)	weeks (fed)		20)		
Rifabutin	1,200 mg twice daily	5	$\leftrightarrow$	↓ 15	↓ 15
300 mg once daily for	for 10 days			(1 28 to 0)	(↓ 38 to ↑ 17)
10 days					
Rifampin	1,200 mg twice daily	11	↓70	↓ 82	↓ 92
300 mg once daily for	for 4 days	l	(↓ 76 to ↓	(↓ 84 to ↓ 78)	(↓ 95 to ↓ 89)
4 days			62)		
Saquinavir	750 or 800 mg 3	7	↓ 37	↓ 32	↓14
800 mg 3 times a day for	times a day for 2		(↓ 54 to ↓	( ↓ 49 to ↓ 9)	(↓ 52 to ↑ 54)
2 weeks (fed)	weeks (fed)		14)		
Zidovudine	600-mg	12	$\leftrightarrow$	↑ 13	NA
300-ma sinale dose	single dose	i		(   2 to ↑ 31)	ı .

(↓ 2 to ↑ 31) 300-mg single dose single dose Compared with parallel control group.

Median percent change; confidence interval not reported. hanne († or 1 Jess than 10%): NA = C.... not calculated for single-dose tria

Coadministered Drug(s)	Dose of Fosamprenavir		% Change in Pharmacokinetic Parameter Coadministered Drug (90% CI)				
and Dose(s)	Calcium *	n	Cmax	AUC	Cmin		
Atazanavir	700 mg twice daily plus	21	↓ 24	↓ 22	↔		
300 mg once daily	ritonavir 100 mg twice	l	(↓ 39 to ↓ 6)	(↓ 34 to ↓ 9)			
for 10 days <sup>b</sup>	daily for 10 days	16					
Atorvastatin	1,400 mg twice daily for 2 weeks	16	↑ 304	↑ 130	↓10		
10 mg once daily for 4 days	IOF 2 Weeks	l	(↑ 205 to ↑ 437)	(↑ 100 to ↑ 164)	(↓ 27 to ↑ 12)		
Atorvastatin	700 mg twice daily plus	16	184	↑ 153	↑ 73		
10 mg once daily	ritonavir 100 mg twice		(↑ 126 to ↑	(↑ 115 to ↑ 199)	(↑ 45 to ↑ 108)		
for 4 days	daily for 2 weeks		257)		,, ,		
Esomeprazole	1,400 mg twice daily	25	↔	↑ 55	ND		
20 mg once daily	for 2 weeks	l		(↑ 39 to ↑ 73)			
for 2 weeks Esomeprazole	700 mg twice daily plus	23			ND		
20 mg once daily	ritonavir 100 mg twice	23	↔	↔	ND		
for 2 weeks	daily for 2 weeks	l					
Ethinyl estradiol <sup>c</sup>	700 mg twice daily plus	25	↓ 28	↓ 37	ND		
0.035 mg once	ritonavir 100 mg twice	l	(↓ 21 to ↓ 35)	(↓ 30 to ↓ 42)	I		
daily for 21 days	daily for 21 days						
Dolutegravir 50 mg once dailv	700 mg twice daily plus ritonavir 100 mg twice	12	↓24 (↓8 to ↓37)	↓35 (↓22 to ↓46)	↓49 (↓37 to ↓59)		
once daily	daily.	l					
Ketoconazole <sup>d</sup>	700 mg twice daily plus	15	↑ 25	↑ 169	ND		
200 mg once daily	ritonavir 100 mg twice	l	(↑ 0 to ↑ 56)	(↑ 108 to ↑ 248)	""		
for 4 days	dailyfor 4 days	l	(1 1 )	(1,			
Lopinavir/ritonavire	1,400 mg twice daily	18	↔1	↔¹	↔¹		
533 mg/133 mg twice daily for	for 2 weeks	l					
2 weeks		l					
Lopinavir/ritonavire	700 mg twice daily plus	18	↑ 30	↑ 37	↑ 52		
400 mg/100 mg	ritonavir 100 mg twice		(⊥ 15 to ↑ 47)	(⊥ 20 to ↑ 55)	(⊥ 28 to ↑ 82)		
twice daily for	daily for 2 weeks	l	(4 ,	(4 , ,	(4 , - ,		
2 weeks							
Maraviroc 300 mg twice daily	700 mg twice daily plus ritonavir	14	↑ 52 (↑ 27 to ↑ 82)	↑ 149 (↑ 119 to ↑ 182)	↑ 374 (↑ 303 to ↑ 457)		
or 10 days	100 mg twice daily for	l	(† 27 to † 82)	(† 11910 † 182)	(† 303 10 † 457)		
or ro days	20 days	l					
Maraviroc	1,400 mg once daily	14	↑ 45	↑ 126	↑80		
300 mg once daily for	plus ritonavir	l	(↑ 20 to ↑ 74)	(↑ 99 to ↑ 158)	(↑ 53 to ↑ 113)		
10 days	100 mg once daily for	l					
Vlethadone	20 days 700 mg twice daily plus	10		R-Methadone (activ	2)		
70 to 120 mg once	ritonavir 100 mg twice	19	⊥ 21°	18° ↓ 18°	⊥ 11°		
daily for 2 weeks	daily for 2 weeks	l	(⊥ 30 to ⊥ 12)	(⊥ 27 to ⊥ 8)	(⊥ 21 to ↑ 1)		
	_	l		-Methadone (inacti			
		l	↓ 430	↓ 43°	↓ 41°		
	4 400	17	(↓ 49 to ↓ 37)	(↓ 50 to ↓ 36)	(↓ 49 to ↓ 31)		
Nevirapine 200 mg twice daily	1,400 mg twice daily for 2 weeks	17	↑ 25 (↑ 14 to ↑ 37)	↑ 29 (↑ 19 to ↑ 40)	↑ 34 (↑ 20 to ↑ 49)		
for 2 weeksh	IUI 2 Weeks	l	(  1410   37)	(  1910   40)	(  20 10   49)		
Nevirapine	700 mg twice daily plus	17	↑13	↑14	↑ 22		
200 mg twice daily	ritonavir 100 mg twice	l	(↑ 3 to ↑ 24)	(↑ 5 to ↑ 24)	(↑ 9 to ↑ 35)		
for 2 weeks <sup>h</sup>	daily for 2 weeks						
Norethindrone <sup>c</sup> 0.5 mg once daily	700 mg twice daily plus ritonavir 100 mg twice	25	↓38 (⊥ 32 to ⊥ 44)	↓ 34 (⊥ 30 to ⊥ 37)	↓ 26 (↓ 20 to ↓ 32)		
for 21 days	daily for 21 days	l	(1 32 10 1 44)	(1 30 10 1 37)	(1 20 10 1 32)		
Phenytoin	700 mg twice daily plus	14	120	1.22	129		
300 mg once daily	ritonavir 100 mg twice	l	( 12 to ↓ 27)	( 17 to 127)	( 23 to 134)		
for 10 days	daily for 10 days	L			,, ,		
Rifabutin	700 mg twice daily plus	15	↓14 (: 00 t · 4)	$\leftrightarrow$	↑ 28		
150 mg every other day for 2 weeks i	ritonavir 100 mg twice daily for 2 weeks	l	(↓ 28 to ↑ 4)		(↑ 12 to ↑ 46)		
-	ually for 2 weeks	l					
(25-0-		l	↑ 579	↑ 1,120	↑ 2,510		
desacetylrifabutin	l	ı	(† 479 to † 698)	(↑ 965 to ↑ 1,300)	(† 1,910 to		
metabolite)		l	1 090)	1,300)	↑ 3,300)		

Comparison arm of atazanavir 300 mg once daily plus ritonavir 100 mg once daily for 10 days Administered as a combination oral contraceptive tablet: ethinyl estradiol 0.035 mg/norethindrone 0.5 mg. Subjects were receiving fosamprenavir calcium/ritonavir for 10 days prior to the 4-day treatment period with both ket

700 mg twice daily plus ritonavir 100 mg twice daily

Rifabutin + 25-0-desacetylrifabutin metabolite

Compared with lopinavir 400 mg/ritonavir 100 mg twice daily for 2 weeks Dose normalized to methadone 100 mg. The unbound concentration of the active moiety, R-methadone, was unchanged Subjects were receiving nexisquies for at least 12 weeks prior to trial.

The subjects were receiving nexisquies for at least 12 weeks AUC is AUC<sub>(0-8.7)</sub>.

The nexass, 1 - Decrease, -- I no change (1 or 1 less than 10%), ND = Interaction cannot be determined as C<sub>min</sub> was below the lower limit of quantitation.

**─** 

↑ 64 (↑ 46 to ↑ 84)

(1 8)

Coadministered Drug(s)	Dose of		% Change in Pharmacokinetic Parameters Coadministered Drug (90% CI)		
and Dose(s)	AGENERASE	n	Cmax	AUC	Cmin
Abacavir 300 mg twice daily for 2 to 3 weeks	900 mg twice daily for 2 to 3 weeks	4	$\leftrightarrow^a$	↔8	↔ <sup>8</sup>
Clarithromycin 500 mg twice daily for 4 days	1,200 mg twice daily for 4 days	12	↓ 10 (↓ 24 to ↑ 7)	$\leftrightarrow$	$\leftrightarrow$
Delavirdine 600 mg twice daily for 10 days	600 mg twice daily for 10 days	9	↓ 47°	↓ 61°	↓ 88°
Ethinyl estradiol 0.035 mg for 1 cycle	1,200 mg twice daily for 28 days	10	<b>↔</b>	↔	↑ 32 (↓ 3 to ↑ 79)
Indinavir 800 mg 3 times a day for 2 weeks (fasted)	750 mg or 800 mg 3 times a day for 2 weeks (fasted)	9	↓ 22ª	↓ 38ª	↓ 27ª
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	$\leftrightarrow$	↔	NA
Methadone	1,200 mg twice	16	16 R-Methadone (active)		re)
44 to 100 mg once daily for > 30 days	daily for 10 days		(↓ 32 to ↓ 18) (↓ 21 to ↓ 5) (↓ 32 to S-Methadone (inactive)		↓ 21 (↓ 32 to ↓ 9)
> 30 days					Ve)
			(↓ 55 to ↓ 40)	(↓ 46 to ↓ 32)	(↓ 60 to ↓ 43)
Nelfinavir 750 mg 3 times a day for 2 weeks (fed)	750 mg or 800 mg 3 times a day for 2 weeks (fed)	6	↑ 12ª	↑ 15ª	↑ 14ª
Norethindrone 1 mg for 1 cycle	1,200 mg twice daily for 28 days	10	<b>+</b>	↑ 18 (↑ 1 to ↑ 38)	↑ 45 (↑ 13 to ↑ 88)
Rifabutin 300 mg once daily for 10 days	1,200 mg twice daily for 10 days	5	↑119 (↑ 82 to ↑ 164)	↑193 (↑ 156 to ↑ 235)	↑ 271 (↑ 171 to ↑ 409)
Rifampin 300 mg once daily for 4 days	1,200 mg twice daily for 4 days	11	$\leftrightarrow$	$\leftrightarrow$	ND

Table 13. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir after Administrat

mg 3 times a day

800 mg 3 times a day for

was below the lower limit of quantitation.

12.4 Microbiology
Mechanism of Action
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. of viral Gag and Gag-Pot polyprotein precursors, resulting in the formation of immature non-innectious 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 lympholostic cell lines (MT-4, CEM-CORF, H9) and in prepileral blood bympholostic in cell culture. The 50% effective concentration (ECs<sub>20</sub>) 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 mag per mL). The median ECs<sub>20</sub> value of amprenavir against HIV-1 isolates from clades A to G was 0.00095 microM in principated blood mononuclear cells (PBMOs, Similarly, the ECs<sub>20</sub> values for magneravir against monocytes/macrophage tropic HIV-1 isolates (clade B) ranged from 0.003 to 0.075 microM in monocyte/macrophage cultures. The ECs<sub>20</sub> values for admitted the control of amprenaviral values of amprenav microM. The anti-HIV-1 activity of amprenavir was not antagonistic in combination with the nucleoside reverse transcriptase inhibitors (NRTIs); abacavir, didanosine, lamivuline, etavudine, tenorlovir, and zidvovdine; the non-nucleoside reverse transcriptase inhibitors (NRTIs) delavirdine, etavirenz, and nevirapine; the protease inhibitors (PIs) atazanavir, indinavir, (pionavir, nelmavir, ritonavir, and saquinavir, and the gp41 fusion inhibitor enfuvirtide. These drug combinations have not been adequately studied in humans.

Saquinavir, and the gp41 fusion inhibitor enfuvirtide. These drug combinations have not been abequately studied in minimals. 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 substitution similarity at positions V321, M46/LI, 4TV, 150V, 154/LM 48/V, 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 fosamprenavir calcium.
Off the 488 antiretroviral-naive subjects treated with fosamprenavir calcium, off my twice daily or fosamprenavir calcium 1,400 mg plus ritonavir 200 mg once daily in Trais APV30001 and APV30002, respectively, isolates from 61 subjects (29 receiving fosamprenavir calcium and 32 receiving fosamprenavir calcium/ritonavir) with virologic failure (plasma HIV-1 RNA greater than 1,000 copies per mL on 2 occasions on or after Meek 12) were genotyped. Isolates from 5 of the 29 antiretroviral-naive subjects (17%) receiving fosamprenavir calcium without ritonavir in Trai APV30001 had evidence of genotypic resistance to amprenavir. IS-LM (n = 2), IS4L + L35F (n = 1), V321 + I47V (n = 1). No amprenavir resistance-associated substitutions were detected in isolates from 1 virologic failure subject receiving fosamprenavir calcium/ritonavir once daily at Week 160 (HIV-1 RNA greater than 00 copies per mL). Upon retrospective analysis of stored samples using an ultrasensitive assay, these resistant substitutions were detected in isolates from 1 virologic trailure subjects for stored samples using an ultrasensitive assay, these resistant substitutions were detected in isolates from 1 virologic trailure and 100 copies per mL). Upon retrospecti ing degrees of cross-resistance among HIV-1 protease inhibitors have been observed. An association between virologic response al

48 weeks (HIV-T RIVA level less than 400 copies per mL) and protease inhibitor-resistance substitutions detected in baseline HIV-T is localess from protease inhibitor-experienced subjects receiving fosamprenavir calcium /ritonavir twice daily (n = 88), or lopinavir/ritonavir vice daily (n = 88) in Trial APV300013 is shown in Table 14. The majority of subjects had previously received either on et 47%) or 2 protease inhibitors (36%), most commonly nelfinavir (57%) and indinavir (53%). Out of 102 subjects with baseline phenotypes receiving twicedaily fosamprenavir calcium/ritonavir, 54% (n = 55) had resistance to at least one protease inhibitor, with 98% (n = 54) of those having

Protease Inhibitor Resistance-Associated	Fosamprenavir Calcium/Ritonavir Twice Daily		Lopinavir/Rito	navir Twice Daily
Substitutions <sup>b</sup>	(n =	= 88)	(n	= 85)
030N	21/22	95%	17/19	89%
188D/S	20/22	91%	12/12	100%
90M	16/31	52%	17/29	59%
1461/L	11/22	50%	12/24	50%
82A/F/T/S	2/9	22%	6/17	35%
54V	2/11	18%	6/11	55%
84V	1/6	17%	2/5	40%

<sup>b</sup> 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 The virologic response based upon baseline phenotype was assessed. Baseline isolates from protease inhibitor-experienced subjects responding to fosamprenavir calcium/ironavir twice daily had a median shift in susceptibility to an 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 1.4 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 fosamprenavir calcium. Isolates from 15 of the 20 subjects receiving twice-daily fosamprenavir calcium/ironavir up to Week 48 and experiencing virologic alture/longoing replication were subjected to generotypic analysis. The following apprenavir resistance-associated substitutions were found either alone or in combination: V32, IM46IL, 147V, 150V, 154UM, and 184V. Isolates from 4 of the 16 subjects continuing to receive wice-daily fosamprenavir calcium/ironavir up to Week 96 who experienced virologic failure underwort genotypic analysis. Isolates from 2 subjects contained amprenavir resistance-associated substitutions: V32I, M46I, and 147V in 1 isolate and 184V in the other.

13 NONCLINICAL TOXICOLOGY

13. NONCLINICAL IUARGUESS.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In Iong-term carcinogenicity, studies, fosamprenavir was administered orally for up tr
per day in mice and at doses of 300, 825, or 2,250 mg per kg per day in rafs. Expos stered orally for up to 104 weeks at doses of 250, 400, or 600 mg per kg (rats) those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcir 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 twic daily. There was an increase in hepatocellular adenomas and hepatocellular carcinomas at all doses in male mice and at 600 mg per k per day in female mice, and in hepatocellular adenomas and thyroid follicular cell adenomas at all does in male rats, and an day of male rats, and in hepatocellular adenomas and thyroid follicular cell adenomas at all does 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 numans, to thyroid neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at 825 mg per kg per day an 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 endometri findings was slightly increased over concurrent controls, but was within background range for female rats. The relevance of the uterin 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 rosamprenavir was not intulagenic or genoloxic in a battery of in wird and in who assays. These assays included caterial reviews emitation (Ames), mouse lymphoma, at micronucleus, and chromosome aberrations in human hymphocytes. 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) and female rats (treated for 2 weeks before mating) frough Postpartum Day 6) that received doses of 300, 820, or 2,240 mp per kg per day. Systemic exposures (AUC<sub>0-246</sub>) 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 fritonavir. 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.

14 CLINICAL STUDIES

Table 15. Outcomes of Randomized Treatment through Week 48 (APV30001

14.1 Therapy-Naive Adult trials
APV30001
A randomized, open-label trial evaluated treatment with fosamprenavir calcium 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 lamivadine (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 writhig, 25% were black, and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells per mm<sup>3</sup> (range: 2 to 1.136 cells per mm<sup>3</sup>, 18% of subjects had a CD4+ cell count of less than 50 cells per mm<sup>3</sup> and 30% were in the range of 50 to less than 200 cells per mm<sup>3</sup>). Baseline median HIV-1 RNA was 4.83 logn copies per mL (range: 1.69 to 7.41 logno copies per mL; 45% of subjects had greater than 100,000 copies per mL).

The outcomes of randomized treatment are provided in Table 15.

Outcome (Rebound or discontinuation = failure) 1,250 mg Twice Daily (n = 83)

	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 <sup>b</sup>	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 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.					

Screening Viral Load HIV-1 RNA (copies/mL)	Fosamprenavir Calcium 1,400 mg Twice Daily		Nelfinavir 1,250 mg Twice Daily	
	< 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 in osamprenavir calcium and 216 cells per mm APV30002	<sup>3</sup> in the nelfinavir group.		,	
A randomized, open-label trial evaluated treatment with fosamprenavir calcium 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) versus neilinavir (1,250 mg twice daily) i daily) and lamivudine (150 mg twice daily).	in 649 treatment-naive subjects. Both treat	iment group	s also received abacavir (300	rng twice
duly) and lamifoldino (100 mg timos daily).	07 ( 40   00 ) 700/		1 000/ 000	

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 of less per mm<sup>5</sup> (range: 1 to 1,055 cells per mm<sup>5</sup> (20% of subjects had a CD4+ cell count of less than 50 cells per mm<sup>5</sup> (and 20% of less than 50 cells per mm<sup>5</sup>). Baseline median HV1-1 RNA was 4.81 log<sub>10</sub> copies per mL (range: 2.65 to 7.29 log<sub>10</sub> copies per mL; 43% of subjects had greater than 100,000 copies per mL). The outcomes of randomized treatment are provided in Table 17. Table 17. Outcomes of Randomized Treatment through Week 48 (APV30002)

Outcome (Rebound or discontinuation = failure)	Fosamprenavir Calcium 1,400 mg/ Ritonavir 200 mg Once Daily (n = 322)	Nelfinavir 1,250 mg Twice Daily (n = 327)	
Responder <sup>a</sup>	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 <sup>b</sup>	15%	10%	
<sup>a</sup> Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per mL (less than 50 copies per mL) through Week 48 (Roche AMPLIC			

Support authered and international commitment of internations are not copies per int. (less dail of copie IHIV-1 MONITOR Assay Version 1.5).

Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other reasons. Freatment response by viral load strata is shown in Table 18.

Table 18. Proportions of Responders through Week 48 by Screening Viral Load (APV30002) Fosamprenavir Calcium 1,400 mg/Ritonavir 200 mg Once Daily 1,250 mg Twice Daily rrough 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 203 cells per mm³ in the group receivin samprenavir calcium and 207 cells per mm³ in the nelfinavir group. APV30003
A randomized, open-label, multicenter trial evaluated 2 different regimens of fosamprenavir calcium plus ritonavir (fosamprenavir calcium tables 1 400 mo once daily plus ritonavir 200 m

tablets 700 mg twice daily plus ritonavir 100 mg twice daily or fosamprenavir calcium 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 ordease 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. 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 mm³ (range: 2 to 1,171 cells per mm³). Baseline median plasma HIV-1 RNA level was 4.1 d log<sub>10</sub> copies per mL (range: 1.69 to 6.41 log<sub>10</sub> copies per mL). The median durations of prior exposure to NRT1s were 257 weeks for subjects receiving fosampenavir calculm/rinonavir twice daily (79% had greater than or equal to 3 prior NRT1s) and 210 weeks for subjects receiving lopinavir/ritonavir (64% had greater than or equal to 3 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 losamprenavir calcium/ritonavir twice claily (49% received greater than or equal to 2 prior protease inhibitors) and 130 weeks for subjects receiving losamprenavir calcium/ritonavir (40% received greater than or equal to 2 prior protease inhibitors). The time-averaged changes in plasma HIV-1 RIMA from baseline (AbLOMB) at 48 weeks (the endpoint on which the trial was powered) were -1.4 log<sub>10</sub> copies per mL for twice-daily tosamprenavir calcium/ritonavir and -1.67 log<sub>10</sub> copies per mL for the lopinavir/ritonavir group. The proportions of subjects who achieved and maintained confirmed HIV-1 RIM laes than 400 copies per mL for the lopinavir/ritonavir group. The proportions of subjects with a HIV-1 RIMA less than 50 copies per mL with twice-daily fosamprenavir calcium/ritonavir and 61% with lopinavir/ritonavir group. The proportions of subjects with HIV-1 RIMA less than 50 copies per mL with twice-daily fosamprenavir calcium/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 fosamprenavir calcium/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 mm³ with twice-daily fosamprenavir calcium/ritonavir and lopinavir/ritonavir are clinically equivalent.

equivalent.

Once-daily administration of fosamprenavir calcium plus ritonavir is not recommended for protease inhibitor-experienced patients. Through Week 48, 50% and 37% of subjects receiving fosamprenavir calcium 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.

14.3. Pediatric Trials

Three open-label trials in pediatric subjects aged at least 4 weeks to 18 years were conducted. In one trial (APV29005), twice-daily dosing Infee open-table trials in pediants (suplests aged at least 4 weeks to 1s years were conducted. In one trial (APV29UDs), twice-daily dosing regimens (fosamprenavir calcium with or without ritonavir) were evaluated in combination with other antiretroving agents in pediatric subjects aged 2 to 18 years. In a second trial (APV20002), twice-daily dosing regimens (fosamprenavir calcium with ritonavir) were evaluated in combination with other antiretrovinal agents in pediatric subjects aged at least 4 weeks to younger that (APV20003) evaluated once-daily dosing of fosamprenavir calcium with ritonavir, the pharmacokinetic data from this trial did not support a once-daily dosing regimen in any pediatric patient population.

APV29005

APV29005
Fosamprenavir calcium: Twenty (18 therapy-naive and 2 therapy-experienced) pediatric subjects received fosamprenavir calcium oral suspension without ritonavir twice daily. At Week 24, 65% (13 of 20) achieved HIV-1 RNA less than 400 copies per mL, and the median increase from baseline in CD4+ cell count was 350 cells per mm<sup>3</sup>. Fosamprenavir calcium plus \*Nitonavir\*. Forty-nine protease inhibitor-rave and 40 protease inhibitor-experienced pediatric subjects received fosamprenavir calcium profit suspension or tablets with ritonavir twice daily. At Week 24, 71% of protease inhibitor-navie (35 of 49) and 55% of protease inhibitor-experienced (22 of 40) subjects caheived HIV-1 RNA lies sthan 400 copies per mC, median increases from baseline in CD4+ cell counts were 184 cells per mm³ and 150 cells per mm³ in protease inhibitor-naive and experienced subjects, respectively. APV20002 LOH+ cell culturis were the core partitudes.

APV20002

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

16 HOW SUPPLIED/STORAGE AND HANDLING Fosamprenavir calcium tablets, 700 mg, are pink colored, coated, oval-shaped tablets with "RJ47" imprinted on one side with black ink and plain on the other side. They are supplied as follows-Bottles of 30 with child-resistant closure Bottles of 60 with child-resistant closure

Store at 20° C to 25° C (68° F to 77° F) [See USP Controlled Room Temperature] 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

<u>Drug Interactions</u>

A statement to patients and healthcare providers is included on the product's bottle label: ALERT: Find out about medicines that should Astatement to patients and meditated providers is included on the products some table. ALEEN: Find out about medicines that should NOT be taken with fosampenavir calcium tablets. Fosamprenavir calcium tablets may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, particularly St. John's wort. Advise patients receiving PDE5 inhibitors that they may be at an increased risk of PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapsies, and should promptly report any symptoms to their healthcare provider [see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7)]. <u>...</u> nts receiving combined hormonal contraception to use an effective alternative contraceptive method or an additional barrier

method during therapy with fosamprenavir calcium tablets because hormonal levels may decrease, and if used in combination with fosamprenavir calcium tablets and ritonavir, liver enzyme elevations may occur [see Drug Interactions (7.2), Use in Specific Populations <u>Sulfa Allergy</u>
Advise patients to inform their healthcare provider if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the Severe Skin Reactions
Advise patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, have been reported with
Advise patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, have been reported with

fosamprenavir calcium tablets. Advise patients to discontinue fosamprenavir calcium tablets immediately for severe or life-threatening skin reactions or for moderate rashes accompanied by systemic symptoms [see Warnings and Precautions (5.2), Adverse Reactions (6)]. Hepatic Toxicity

Advantage patients that it is recommended to have laboratory testing before and during therapy as patients with underlying hepatitis B or C or marked elevations of transaminases prior to treatment may be at increased risk for developing or worsening transaminase elevations with use of fosamprenavir calcium tablets, particularly at higher than recommended doses which should not be used. [see Warnings and Countries of the Countr Immune Reconstitution Syndrome
Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when fosamprenavir calcium tablets is started [see Warnings and Precautions (5.6)].

and Prezautions (3.0).
Increase in Body Tat
Inform patients that an increase of body fat may occur in patients receiving protease inhibitors, including fosamprenavir calcium tablets,
and that the cause and long-term health effects of these conditions are not known at this time [see Warnings and Precautions (5.7)]. <u>Lipid Elevations</u>

Advise patients that it is recommended to have laboratory testing before and during therapy as increases in the concentration of triglycerides and cholesterol have been reported with use of fosamprenavir calcium tablets [see Warnings and Precautions (5.8), Adverse Reactions (6)] Pregnancy Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to fosamprenavir calcium tablets during pregnancy (see Use in Specific Populations (8.1)). <u>caccaron.</u> Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *Isee Use in Specific* 

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