CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-007/SE7-006
21-039/SE7-006

Final Printed Labeling

AGENERASE®

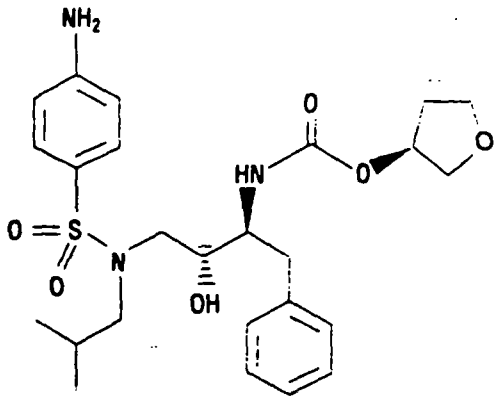
(amprenavir)

Capsules

PATIENT INFORMATION INCLUDED

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol contained in **AGENERASE Oral Solution**, that formulation is contraindicated in infants and children below the age of 4 years and certain other patient populations and should be used with caution in others. Consult the complete prescribing information for **AGENERASE Oral Solution** for full information.

DESCRIPTION: AGENERASE (amprenavir) is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3*S*)-tetrahydro-3-furyl *N*-[(1*S*,2*R*)-3-(4-amino-*N*-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{35}N_3O_6S$ and a molecular weight of 505.64. It has the following structural formula:



Amprenavir is a white to cream-colored solid with a solubility of approximately 0.04 mg/mL in water at 25°C.

AGENERASE Capsules are available for oral administration in strengths of 50 and 150 mg. Each 50-mg capsule contains the inactive ingredients d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg, and propylene glycol 19 mg. Each 150-mg capsule contains the inactive ingredients TPGS, PEG 400 740 mg, and propylene glycol 57 mg. The capsule shell contains the inactive ingredients d-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink. Each 150-mg AGENERASE Capsule contains 109 IU vitamin E in the form of TPGS. The total amount of vitamin E in the recommended daily adult dose of AGENERASE is 1744 IU.

MICROBIOLOGY:

Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity *in Vitro*: The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). Amprenavir exhibited synergistic anti-HIV-1 activity in combination with abacavir, zidovudine, didanosine, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro* and obtained from patients treated with amprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V as well as mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1 isolates from 21 nucleoside reverse transcriptase inhibitor- (NRTI-) experienced, protease inhibitor-naive patients treated with amprenavir in combination with NRTIs for 16 to

48 weeks identified isolates from 15 patients who exhibited a 4- to 17-fold decrease in susceptibility to amprenavir *in vitro* compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored one or more amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation.

Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. Five of 15 amprenavir-resistant isolates exhibited 4- to 8-fold decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were susceptible to either indinavir or saquinavir.

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.

Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (t_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1200 mg were slightly greater than dose proportional. Increases in AUC were dose proportional after 3 weeks of dosing with doses from 300 to 1200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1200 mg b.i.d. for 3 weeks to HIV-infected subjects are shown in Table 1.

Table 1: Average (%CV) Pharmacokinetic Parameters After 1200 mg b.i.d. of Amprenavir Capsules (n = 54)

C_{max} (mcg/mL)	t_{max} (hours)	AUC_{0-12} (mcg•h/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE Capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single 1200-mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C_{max} (fed: 6.18 ± 2.92 mcg/mL, fasted: 9.72 ± 2.75 mcg/mL), t_{max} (fed: 1.51 ± 0.68, fasted: 1.05 ± 0.63), and $AUC_{0-\infty}$ (fed: 22.06 ± 11.6 mcg•h/mL, fasted: 28.05 ± 10.1 mcg•h/mL). AGENERASE may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION).

Distribution: The apparent volume of distribution (V_z/F) is approximately 430 L in healthy adult subjects. *In vitro* binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is alpha$_1$-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to 10.6 hours.

Special Populations: ***Hepatic Insufficiency:*** AGENERASE has been studied in adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•h/mL). The $AUC_{0-\infty}$ and C_{max} were significantly

greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•h/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$: 12.00 ± 4.38 mcg•h/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The impact of renal impairment on amprenavir elimination in adult patients has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients: The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The $AUC_{0-\infty}$ increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore **AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis.**

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the large amount of the excipient propylene glycol. Please see the complete prescribing information for **AGENERASE Oral Solution** for full information.

Table 2: Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years Receiving 20 mg/kg b.i.d. or 15 mg/kg t.i.d. of AGENERASE Oral Solution

Dose	n	C_{max} (mcg/mL)	t_{max} (hours)	AUC_{ss}* (mcg•h/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
20 mg/kg b.i.d.	20	6.77 (51%)	1.1 (21%)	15.46 (59%)	1.29 (59%)	0.24 (98%)	29 (58%)
15 mg/kg t.i.d.	17	3.99 (37%)	1.4 (90%)	8.73 (36%)	1.09 (36%)	0.27 (95%)	32 (34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C_{avg} is a better comparison of the exposures.

Geriatric Patients: The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender: The pharmacokinetics of amprenavir do not differ between males and females.

Race: The pharmacokinetics of amprenavir do not differ between Blacks and non-Blacks.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of amprenavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS.

Table 3: Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in Amprenavir Pharmacokinetic Parameters* (90% CI)		
				C_{max}	AUC	C_{min}
Abacavir	300 mg b.i.d. for 3 weeks	900 mg b.i.d. for 3 weeks	4	↑47 (↓15 to ↑154)	↑29 (↓18 to ↑103)	↑27 (↓46 to ↑197)
Clarithromycin	500 mg b.i.d. for 4 days	1200 mg b.i.d. for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole	400 mg single dose	1200 mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	⇔ (↓17 to ↑9)	⇔ (↓15 to ↑14)	NA
Nelfinavir	750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	⇔ (↓19 to ↑47)	↑189 (↑52 to ↑448)
Rifabutin	300 mg q.d. for 10 days	1200 mg b.i.d. for 10 days	5	⇔ (↓21 to ↑10)	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifampin	300 mg q.d. for 4 days	1200 mg b.i.d. for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir	800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine	300 mg single dose	600 mg single dose	12	⇔ (↓5 to ↑24)	↑13 (↓2 to ↑31)	NA

*Based on total-drug concentrations.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study.

Table 4: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
				C_{max}	AUC	C_{min}
Clarithromycin	500 mg b.i.d. for 4 days	1200 mg b.i.d. for 4 days	12	↓10 (↓24 to ↑7)	⇔ (↓17 to ↑11)	⇔ (↓13 to ↑20)
Ketoconazole	400 mg single dose	1200 mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	⇔ (↓17 to ↑3)	⇔ (↓11 to 0)	NA
Rifabutin	300 mg q.d. for 10 days	1200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin	300 mg q.d. for 4 days	1200 mg b.i.d. for 4 days	11	⇔ (↓13 to ↑12)	⇔ (↓10 to ↑13)	ND
Zidovudine	300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA

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

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE: AGENERASE (amprenavir) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with AGENERASE:

In a study of NRTI-experienced, protease inhibitor-naive patients, AGENERASE was found to be significantly less effective than indinavir (see Description of Clinical Studies).

Mild to moderate gastrointestinal adverse events led to discontinuation of AGENERASE primarily during the first 12 weeks of therapy (see ADVERSE REACTIONS).

There are no data on response to therapy with AGENERASE in protease inhibitor-experienced patients.

Description of Clinical Studies: ***Therapy-Naive Adults:*** PROAB3001, a randomized, double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) in 232 patients. Through 24 weeks of therapy, 53% of patients assigned to AGENERASE/zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Through week 48, the antiviral response was 41%. Through 24 weeks of therapy, 11% of patients assigned to zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Antiviral response beyond week 24 is not interpretable because the majority of patients discontinued or changed their antiretroviral therapy.

NRTI-Experienced Adults: PROAB3006, a randomized, open-label multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus NRTIs versus indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80% male, with a median CD4 cell count of 404 cells/mm^3 (range 9 to 1706 cells/mm^3) and a median plasma HIV-1 RNA level of 3.93 $\log_{10}$ copies/mL (range 2.60 to

208 7.01 $\log_{10}$ copies/mL) at baseline. Through 48 weeks of therapy, the median CD4 cell count
209 increase from baseline in the amprenavir group was significantly lower than in the indinavir
210 group, 97 cells/mm^3 versus 144 cells/mm^3, respectively. There was also a significant
211 difference in the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL
212 through 48 weeks (see Figure 1 and Table 5).
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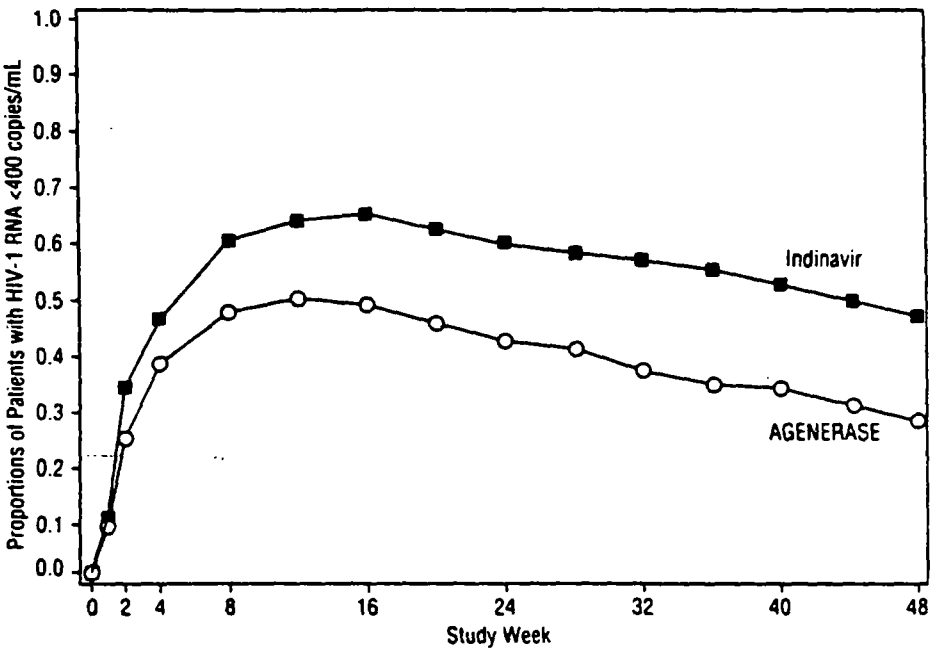
214 **Figure 1: Virologic Response Through Week 48, PROAB3006*,†**



○ AGENERASE plus NRTIs (n = 254)
■ Indinavir plus NRTIs (n = 250)
*Roche AMPLICOR HIV-1 MONITOR assay.
†Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

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217 HIV-1 RNA status and reasons for discontinuation of randomized treatment at 48 weeks
218 are summarized (Table 5).
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Table 5: Outcomes of Randomized Treatment Through Week 48 (PROAB3006)

Outcome	AGENERASE (n = 254)	Indinavir (n = 250)
HIV RNA <400 copies/mL*	30%	49%
HIV RNA ≥400 copies/mL†,‡	38%	26%
Discontinued due to adverse events‡	16%	12%
Discontinued due to other reasons‡,§	16%	13%

*Corresponds to rates at Week 48 in Figure 1.

†Virological failures at or before Week 48.

‡Considered to be treatment failure in the analysis.

§Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations, non-compliance, pregnancy, never treated, and other reasons.

CONTRAINDICATIONS: Coadministration of AGENERASE is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 6.

Table 6: Drugs That are Contraindicated with AGENERASE

Drug Class	Drugs Within Class That Are CONTRAINDICATED with AGENERASE
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hyponotics	Midazolam, triazolam

Because of the potential toxicity from the large amount of the excipient propylene glycol contained in **AGENERASE Oral Solution**, that formulation is contraindicated in certain patient populations and should be used with caution in others. Consult the complete prescribing information for **AGENERASE Oral Solution** for full information.

AGENERASE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

WARNINGS: ALERT: Find out about medicines that should not be taken with AGENERASE.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with AGENERASE (see CONTRAINDICATIONS).

Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of amprenavir by about 90%.

Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including AGENERASE, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.

Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir. are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS: Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil).

Because of the potential toxicity from the large amount of the excipient propylene glycol contained in **AGENERASE Oral Solution**, that formulation is contraindicated in certain

patient populations and should be used with caution in others. Consult the complete prescribing information for **AGENERASE Oral Solution** for full information.

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with AGENERASE (see ADVERSE REACTIONS). Acute hemolytic anemia has been reported in a patient treated with AGENERASE.

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

PRECAUTIONS:

General: AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY: Pediatric Patients).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. AGENERASE should be used with caution in patients with a known sulfonamide allergy.

AGENERASE is principally metabolized by the liver; therefore caution should be exercised when administering this drug to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

Formulations of AGENERASE provide high daily doses of vitamin E (see Information for Patients, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

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

Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors. It is also unknown what effect previous treatment with other protease inhibitors will have on the activity of amprenavir (see MICROBIOLOGY).

Information for Patients: A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with AGENERASE.** A Patient Package Insert (PPI) for AGENERASE Capsules is available for patient information.

Patients treated with AGENERASE Capsules should be cautioned against switching to **AGENERASE Oral Solution** because of the increased risk of adverse events from the large amount of propylene glycol in **AGENERASE Oral Solution**. Please see the complete prescribing information for **AGENERASE Oral Solution** for full information.

Patients should be informed that AGENERASE is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of AGENERASE (amprenavir) are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with AGENERASE can reduce the risk of transmitting HIV to others through sexual contact.

Patients should remain under the care of a physician while using AGENERASE. Patients should be advised to take AGENERASE every day as prescribed. AGENERASE must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or

discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.

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

Patients taking antacids (or the buffered formulation of didanosine) should take AGENERASE at least 1 hour before or after antacid (or the buffered formulation of didanosine) use.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events, including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients receiving hormonal contraceptives should be instructed that alternate contraceptive measures should be used during therapy with AGENERASE.

High-fat meals may decrease the absorption of AGENERASE and should be avoided. AGENERASE may be taken with meals of normal fat content.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE Capsules and Oral Solution exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Drug Interactions.

AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

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364 **Table 7: Drugs That Should Not Be Coadministered with AGENERASE**

Drug Class/Drug Name	Clinical Comment
Antihistamines: Astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: Rifampin	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
HMG Co-Reductase Inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

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366 **Table 8: Established and Other Potentially Significant Drug Interactions:**

367 **Alteration in Dose or Regimen May be Recommended Based on Drug Interaction**

368 **Studies or Predicted Interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: Efavirenz, nevirapine	↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
Non-nucleoside Reverse Transcriptase Inhibitor: Delavirdine	↑Amprenavir	Appropriate doses of the combination with respect to safety and efficacy have not been established
Nucleoside Reverse Transcriptase Inhibitor: Didanosine (buffered		Take AGENERASE at least 1 hour before or after

formulation only)	↓Amprenavir	the buffered formulation of didanosine.
HIV-Protease Inhibitors: Indinavir*, lopinavir/ritonavir, nelfinavir*, ritonavir	↑Amprenavir Amprenavir's effect on other protease inhibitors is not well established.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-Protease Inhibitor: Saquinavir*	↓Amprenavir Amprenavir's effect on saquinavir is not well established.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
	Other Agents	
Antacids	↓Amprenavir	Take AGENERASE at least 1 hour before or after antacids.
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	↑Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with AGENERASE, if available.
Antiarrhythmic: Bepridil	↑Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antifungals: Ketoconazole, itraconazole	↑Ketoconazole ↑Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.
Antimycobacterial: Rifabutin*	↑Rifabutin and rifabutin metabolite	A dosage reduction of rifabutin to at least half the recommended dose is required when AGENERASE and rifabutin are coadministered.* A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium Channel Blockers: Diltiazem, felodipine,		

nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Erectile Dysfunction Agent: Sildenafil	↑Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: Atorvastatin, cerivastatin	↑Atorvastatin, ↑Cerivastatin	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with AGENERASE.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.
Oral Contraceptive: Ethinyl estradiol	Effect on ethinyl estradiol is not known.	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and AGENERASE are coadministered.
Tricyclic Antidepressants: Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with AGENERASE.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

Carcinogenesis and Mutagenesis: Long-term carcinogenicity studies of amprenavir in rodents are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Fertility: The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats. The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

Pregnancy and Reproduction: Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed from 15 days before pairing to day 17 of gestation) and rabbits (dosed from day 8 to day 20 of gestation). In pregnant rabbits, amprenavir administration was associated with abortions and an increased incidence of 3 minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. Systemic exposure at the highest tested dose was approximately one twentieth of the exposure seen at the recommended human dose. In rat fetuses, thymic elongation and incomplete ossification of bones were attributed to amprenavir. Both findings were seen at systemic exposures that were one half of that associated with the recommended human dose.

Pre- and post-natal developmental studies were performed in rats dosed from day 7 of gestation to day 22 of lactation. Reduced body weights (10% to 20%) were observed in the offspring. The systemic exposure associated with this finding was approximately twice the exposure in humans following administration of the recommended human dose. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of amprenavir.

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

AGENERASE Oral Solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content.

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

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

Pediatric Use: Two hundred fifty-one patients aged 4 and above have received amprenavir as single or multiple doses in studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

AGENERASE Capsules have not been evaluated in pediatric patients below the age of 4 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the large amount of the excipient propylene glycol. Please see the complete prescribing information for **AGENERASE Oral Solution** for full information.

Geriatric Use: Clinical studies of AGENERASE 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.

ADVERSE REACTIONS: In clinical studies, adverse events leading to amprenavir discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort), which were mild to moderate in severity.

Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001 and PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a median duration of 10 days. Skin rashes led to amprenavir discontinuation in approximately 3% of patients. In some patients with mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence.

Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson syndrome, occurred in approximately 1% of recipients of AGENERASE (see WARNINGS). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Table 9: Selected Clinical Adverse Events of All Grades Reported in >5% of Adult Patients

Adverse Event	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
	AGENERASE*/ Lamivudine/ Zidovudine (n = 113)	Lamivudine/ Zidovudine (n = 109)	AGENERASE*/ NRTI (n = 245)	Indinavir/NRTI (n = 241)
Digestive				
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
Skin				
Rash	27%	6%	20%	15%
Nervous				
Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
Psychiatric				
Depressive or mood disorders	16%	4%	9%	13%

Among amprenavir-treated patients in Phase 3 studies, 2 patients developed de novo diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

Table 10: Selected Laboratory Abnormalities of All Grades Reported in ≥5% of Adult Patients

Laboratory Abnormality (non-fasting specimens)	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
	AGENERASE/ Lamivudine/ Zidovudine (n = 111)	Lamivudine/ Zidovudine (n = 108)	AGENERASE /NRTI (n = 237)	Indinavir/NRTI (n = 239)
Hyperglycemia (>116 mg/dL)	45%	31%	53%	58%
Hypertriglyceridemia (>213 mg/dL)	41%	27%	56%	52%
Hypercholesterolemia (>283 mg/dL)	7%	3%	13%	15%

In studies PROAB3001 and PROAB3006, no increased frequency of Grade 3 or 4 AST, ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in pediatric patients.

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

DOSAGE AND ADMINISTRATION: AGENERASE may be taken with or without food; however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see CLINICAL PHARMACOLOGY: Effects of Food on Oral Absorption). **Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE Capsules exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).**

Adults: The recommended oral dose of AGENERASE Capsules for adults is 1200 mg (eight 150-mg capsules) twice daily in combination with other antiretroviral agents.

Pediatric Patients: For adolescents (13 to 16 years), the recommended oral dose of AGENERASE Capsules is 1200 mg (eight 150-mg capsules) twice daily in combination with other antiretroviral agents. For patients between 4 and 12 years of age or for patients 13 to 16 years of age with weight of <50 kg, the recommended oral dose of AGENERASE Capsules is 20 mg/kg twice daily or 15 mg/kg 3 times daily (to a maximum daily dose of 2400 mg) in combination with other antiretroviral agents.

Before using **AGENERASE Oral Solution**, the complete prescribing information should be consulted.

AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).

Patients with Hepatic Impairment: AGENERASE Capsules should be used with caution in patients with moderate or severe hepatic impairment. Patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Capsules of 450 mg twice daily, and patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE Capsules of 300 mg twice daily (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency).

HOW SUPPLIED: AGENERASE Capsules, 50 mg, are oblong, opaque, off-white to cream-colored soft gelatin capsules printed with "GX CC1" on one side.

Bottles of 480 with child-resistant closures (NDC 0173-0679-00).

AGENERASE Capsules, 150 mg, are oblong, opaque, off-white to cream-colored soft gelatin capsules printed with "GX CC2" on one side.

Bottles of 240 with child-resistant closures (NDC 0173-0672-00).

Store at controlled room temperature of 25°C (77°F) (see USP).

AGENERASE Capsules are manufactured by
R.P. Scherer
Beinheim, France
for

Licensed from

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

VERTEX

Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

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US Patent Nos. 5,585,397; 5,723,490; and 5,646,180

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Date of Issue RL-no.

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

AGENERASE® (amprenavir) Capsules

ALERT: Find out about medicines that should not be taken with AGENERASE. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH AGENERASE."

Please read this information before you start taking AGENERASE (pronounced ah-GEN-er-ase) Capsules, and re-read it each time you receive your prescription, just in case something has changed. Remember that this information does not take the place of careful discussions with your doctor when you start this medication and at checkups. You should not change or stop your anti-HIV treatment without first talking with your doctor. **You should tell your**

doctor about any drug you are taking or planning to take because taking AGENERASE Capsules with some medications can result in serious or life-threatening problems.

You should not switch from AGENERASE Capsules to **AGENERASE Oral Solution** without talking with your doctor.

What are AGENERASE Capsules?

AGENERASE Capsules are a medication used to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome). AGENERASE Capsules are taken by mouth as soft gel capsules. AGENERASE belongs to a class of anti-HIV medicines called protease inhibitors.

How do AGENERASE Capsules work?

AGENERASE Capsules are used only in combination with other anti-HIV medicines. When used in combination therapy, AGENERASE Capsules may help lower the amount of HIV found in your blood, raise CD4 (T) cell count, and keep your immune system as healthy as possible so that it can help fight infection. However, AGENERASE Capsules do not have these effects in all patients.

What are the side effects of AGENERASE Capsules?

Common side effects of AGENERASE Capsules are nausea, vomiting, diarrhea, rash, and a tingling sensation around the mouth. Severe or life-threatening rash has been reported.

Contact your doctor if you have nausea, vomiting, diarrhea, or rash. Your doctor may be able to help you manage these symptoms. Your doctor will advise you whether your symptoms can be managed on therapy or whether AGENERASE Capsules should be stopped.

This list of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with AGENERASE Capsules. Talk to your doctor promptly about any side effects you have.

How should I take AGENERASE Capsules?

Take AGENERASE Capsules exactly as your doctor prescribes them. The usual dosage for adults and adolescents (at least 13 years of age) is eight 150-mg soft gel capsules twice a day (morning and night), in combination with other anti-HIV medicines.

AGENERASE Capsules can be taken with or without food. However, you should not take AGENERASE with a high-fat meal because this could reduce the effectiveness of AGENERASE Capsules.

What should I do if I miss a dose of AGENERASE Capsules?

To help make sure that your anti-HIV therapy is as effective as possible, be very careful to take all of your medication exactly as your doctor prescribed it and do not skip any doses.

If you miss a dose of AGENERASE Capsules by more than 4 hours, wait and take the next dose at the regularly scheduled time. However, if you miss a dose by fewer than 4 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of AGENERASE Capsules at any one time.

When your supply of AGENERASE Capsules or other anti-HIV drugs starts to run low, arrange to get more from your doctor or pharmacy. It is very important that you take anti-HIV drugs as prescribed by your doctor because the amount of virus in your blood may increase if one or more of the drugs is stopped, even for a short time.

Can AGENERASE Capsules be taken with other medications?

Protease inhibitors, including AGENERASE, may interact with other drugs, including those you take without a prescription. Before you take AGENERASE, tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

MEDICINES YOU SHOULD NOT TAKE WITH AGENERASE

- **You <u>should not take</u> any of the following medications with AGENERASE Capsules because serious or life-threatening problems could occur.***

HALCION® (triazolam)
HISMANAL® (astemizole)
Ergot medications (CAFERGOT® and others)
ORAP® (pimozide)
PROPULSID® (cisapride)
VERSED® (midazolam)
VASCOR® (bepridil)
SELDANE® (terfenadine)

- **You should also not take rifampin** with AGENERASE Capsules because this drug reduces the effectiveness of AGENERASE. Rifampin is also known as: RIFADIN®, RIFAMATE®, RIFATER®, and RIMACTANE®.

- Taking AGENERASE with St. John's Wort (hypericum perforatum, a nonprescription herbal product) or products containing St. John's Wort is not recommended. Talk with your doctor if you are taking or are planning to take St. John's Wort because St. John's Wort may reduce the effect of AGENERASE.

- It is not recommended that you take AGENERASE with the cholesterol-lowering drugs MEVACOR® (lovastatin) or ZOCOR® (simvastatin) because of the possible drug interactions. There is also an increased risk of drug interactions between AGENERASE and LIPITOR® (atorvastatin), and BAYCOL® (cerivastatin). Talk to your doctor if you are taking or are planning to take these or other drugs for lowering cholesterol.

Medicines That Require Dose Adjustments or Special Attention From Your Doctor

- **Serious and/or life-threatening drug interactions can also occur if you take AGENERASE Capsules with any of the following drugs.*** If you need to take any of these drugs, your doctor may closely monitor the amount of drug in your blood to minimize potential problems.

CORDARONE® (amiodarone)
Phenobarbital
TEGRETOL®, CARBATROL® (carbamazepine)
DILANTIN® (phenytoin)
Lidocaine
COUMADIN® (warfarin)

(quinidine) QUINAGLUTE®, CARDIOQUIN®, QUINIDEX®
Antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine), PAMELOR® (nortriptyline), TOFRANIL® (imipramine)

- Tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

- Before you take VIAGRA® (sildenafil) with AGENERASE, talk to your doctor about possible drug interactions and side effects. If you take VIAGRA and AGENERASE together, you may be at increased risk of side effects of VIAGRA such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should seek immediate medical assistance to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you use birth control pills, talk to your doctor about choosing a different type of contraceptive, since AGENERASE may reduce the effectiveness of some birth control pills.

- Because AGENERASE Capsules and Oral Solution contain large amounts of vitamin E, you should not take additional vitamin E while taking AGENERASE.

- **Special considerations:***

  If you take AGENERASE Capsules with MYCOBUTIN® (rifabutin), your doctor will lower the dose of MYCOBUTIN.

  If you take AGENERASE Capsules with VIDEX® (didanosine, ddI) (buffered formulation), take them at least 1 hour apart.

  If you take AGENERASE Capsules with antacids, take them at least 1 hour apart.

Do AGENERASE Capsules cure HIV infection or AIDS?

AGENERASE Capsules do not cure HIV infection or AIDS. At this time we do not know if AGENERASE will help you live longer or have fewer of the medical problems (opportunistic infections) that are associated with HIV infection or AIDS. Because of this, you must be sure to be seen regularly by your healthcare professional.

Do AGENERASE Capsules reduce the risk of passing HIV to others?

No. AGENERASE Capsules, as well as other anti-HIV medications, have not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

Who should not take AGENERASE Capsules?

Do not take AGENERASE Capsules if you have had a serious allergic reaction to AGENERASE or any of its ingredients. If you have liver disease, your dosage of AGENERASE may have to be adjusted.

If you are allergic to sulfa drugs, you should inform your doctor.

Can children take AGENERASE Capsules?

Children from 4 to 12 years of age can take AGENERASE Capsules. Your doctor will tell you if the oral solution or capsule is best for your child. Your child's doctor will decide the right dose based on your child's weight and age. **AGENERASE Oral Solution** should not be used in infants and children below 4 years of age.

Can pregnant women and nursing mothers take AGENERASE?

AGENERASE Capsules have not been studied in pregnant women and the risk to the unborn child is not known. Talk to your doctor if you are pregnant or if you become pregnant while taking AGENERASE.

AGENERASE Oral Solution should not be used in pregnant women.

Mothers with HIV should not breastfeed their infants because HIV in the breast milk can infect the infant.

What other medical conditions should I discuss with my doctor?

Talk to your doctor if you are pregnant or if you become pregnant while you are taking AGENERASE.

Also talk to your doctor if you have hemophilia or problems with your liver or kidneys.

How should I store AGENERASE Capsules?

AGENERASE Capsules should be stored at room temperature and should not be refrigerated.

Other information:

This medication is prescribed for a particular condition. Do not use it for any other condition or give it to anybody else. Keep AGENERASE Capsules and all medicines out of the reach of children.

Ask a healthcare professional any questions you may have about AGENERASE.

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716 Date of Issue RL-no.

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AGENERASE®

(amprenavir)

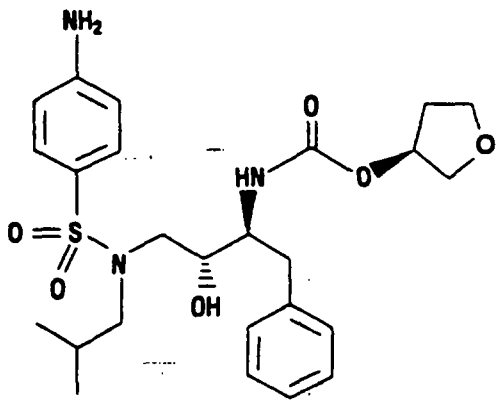
Oral Solution

PATIENT INFORMATION INCLUDED

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

DESCRIPTION: AGENERASE (amprenavir) is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3*S*)-tetrahydro-3-furyl *N*-[(1*S*,2*R*)-3-(4-amino-*N*-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{35}N_3O_6S$ and a molecular weight of 505.64. It has the following structural formula:



Amprenavir is a white to cream-colored solid with a solubility of approximately 0.04 mg/mL in water at 25°C.

AGENERASE Oral Solution is for oral administration. One milliliter (1 mL) of AGENERASE Oral Solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. Each mL of AGENERASE Oral Solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE Oral Solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

MICROBIOLOGY:

Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity *in Vitro*: The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). Amprenavir exhibited synergistic anti-HIV-1 activity in combination with abacavir, zidovudine, didanosine, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro* and obtained from patients treated with amprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V as well as mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1 isolates from 21 nucleoside reverse transcriptase inhibitor- (NRTI-) experienced, protease inhibitor-naive patients treated with amprenavir in combination with NRTIs for 16 to 48 weeks identified isolates from 15 patients who exhibited a 4- to 17-fold decrease in susceptibility to amprenavir *in vitro* compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored one or more amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation.

Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. Five of 15 amprenavir-resistant isolates exhibited 4- to 8-fold decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were susceptible to either indinavir or saquinavir.

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.

Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (t_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1200 mg were slightly greater than dose proportional. Increases in AUC were dose proportional after 3 weeks of dosing with doses from 300 to 1200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1200 mg b.i.d. for 3 weeks to HIV-infected subjects are shown in Table 1.

Table 1: Average (%CV) Pharmacokinetic Parameters After 1200 mg b.i.d. of Amprenavir Capsules (n = 54)

C_{max} (mcg/mL)	t_{max} (hours)	AUC_{0-12} (mcg•h/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE Capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single 1200-mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C_{max} (fed: 6.18 ± 2.92 mcg/mL, fasted: 9.72 ± 2.75 mcg/mL), t_{max} (fed: 1.51 ± 0.68, fasted: 1.05 ± 0.63), and $AUC_{0-\infty}$ (fed: 22.06 ± 11.6 mcg•h/mL, fasted: 28.05 ± 10.1 mcg•h/mL). AGENERASE may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION).

Distribution: The apparent volume of distribution (V_d/F) is approximately 430 L in healthy adult subjects. *In vitro* binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is alpha$_1$-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

AGENERASE Oral Solution contains a large amount of propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Alcohol dehydrogenase (ADH) is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears

that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults. Additionally, certain patient groups (females, Asians, Eskimos, Native Americans) may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to 10.6 hours.

Special Populations: ***Hepatic Insufficiency:*** AGENERASE Oral Solution is contraindicated in patients with hepatic failure.

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with hepatic impairment. AGENERASE Capsules have been studied in adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•h/mL). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•h/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$: 12.00 ± 4.38 mcg•h/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with renal failure.

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. Additionally, because metabolites of the excipient propylene glycol in AGENERASE Oral Solution may alter acid-base balance, patients with renal impairment should be monitored for potential adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with renal impairment. The impact of

renal impairment on amprenavir elimination has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients: AGENERASE Oral Solution is contraindicated in infants and children below 4 years of age (see CONTRAINDICATIONS and WARNINGS).

The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The $AUC_{0-\infty}$ increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore **AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis.**

Table 2: Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years Receiving 20 mg/kg b.i.d. or 15 mg/kg t.i.d. of AGENERASE Oral Solution

Dose	n	C_{max} (mcg/mL)	t_{max} (hours)	AUC_{ss}* (mcg•h/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
20 mg/kg b.i.d.	20	6.77 (51%)	1.1 (21%)	15.46 (59%)	1.29 (59%)	0.24 (98%)	29 (58%)
15 mg/kg t.i.d.	17	3.99 (37%)	1.4 (90%)	8.73 (36%)	1.09 (36%)	0.27 (95%)	32 (34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C_{avg} is a better comparison of the exposures.

Geriatric Patients: The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender: The pharmacokinetics of amprenavir do not differ between males and females. Females may have a lower amount of alcohol dehydrogenase compared with males and may be at increased risk of propylene glycol-associated adverse events; no data are available on propylene glycol metabolism in females.

Race: The pharmacokinetics of amprenavir do not differ between Blacks and non-Blacks. Certain ethnic populations (Asians, Eskimos, and Native Americans) may be at increased risk of propylene glycol-associated adverse events because of alcohol dehydrogenase polymorphisms; no data are available on propylene glycol metabolism in these groups.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of amprenavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS.

186 **Table 3: Drug Interactions: Pharmacokinetic Parameters for Amprenavir**

187 **in the Presence of the Coadministered Drug**

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in Amprenavir Pharmacokinetic Parameters* (90% CI)		
				C_{max}	AUC	C_{min}
Abacavir	300 mg b.i.d. for 3 weeks	900 mg b.i.d. for 3 weeks	4	↑47 (↓15 to ↑154)	↑29 (↓18 to ↑103)	↑27 (↓46 to ↑197)
Clarithromycin	500 mg b.i.d. for 4 days	1200 mg b.i.d. for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole	400 mg single dose	1200 mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	⇔ (↓17 to ↑9)	⇔ (↓15 to ↑14)	NA
Nelfinavir	750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	⇔ (↓19 to ↑47)	↑189 (↑52 to ↑448)
Rifabutin	300 mg q.d. for 10 days	1200 mg b.i.d. for 10 days	5	⇔ (↓21 to ↑10)	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifampin	300 mg q.d. for 4 days	1200 mg b.i.d. for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir	800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine	300 mg single dose	600 mg single dose	12	⇔ (↓5 to ↑24)	↑13 (↓2 to ↑31)	NA.

188 *Based on total-drug concentrations.

189 ↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for

190 single-dose study.

191

Table 4: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

Co-administered Drug	Dose of Co-administered Drug	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
				C_{max}	AUC	C_{min}
Clarithromycin	500 mg b.i.d. for 4 days	1200 mg b.i.d. for 4 days	12	↓10 (↓24 to ↑7)	⇔ (↓17 to ↑11)	⇔ (↓13 to ↑20)
Ketoconazole	400 mg single dose	1200 mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	⇔ (↓17 to ↑3)	⇔ (↓11 to 0)	NA
Rifabutin	300 mg q.d. for 10 days	1200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin	300 mg q.d. for 4 days	1200 mg b.i.d. for 4 days	11	⇔ (↓13 to ↑12)	⇔ (↓10 to ↑13)	ND
Zidovudine	300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA

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

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE: AGENERASE (amprenavir) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with AGENERASE:

- **In a study of NRTI-experienced, protease inhibitor-naive patients, AGENERASE was found to be significantly less effective than indinavir (see Description of Clinical Studies).**
- **Mild to moderate gastrointestinal adverse events led to discontinuation of AGENERASE primarily during the first 12 weeks of therapy (see ADVERSE REACTIONS).**
- **There are no data on response to therapy with AGENERASE in protease inhibitor-experienced patients.**

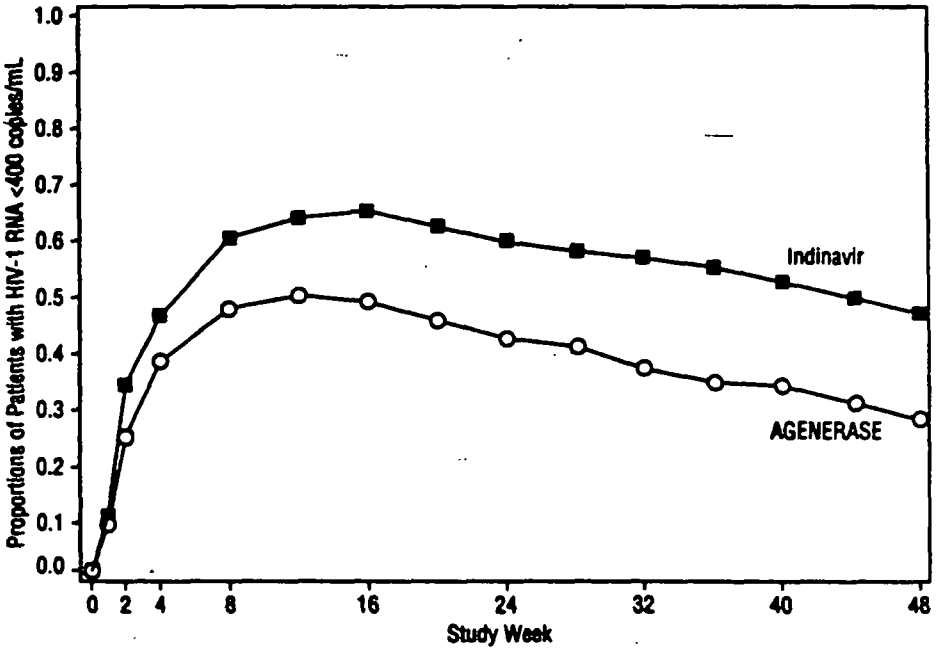
AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Description of Clinical Studies: ***Therapy-Naive Adults:*** PROAB3001, a randomized, double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) in 232 patients. Through 24 weeks of therapy, 53% of patients assigned to AGENERASE/zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Through week 48, the antiviral response was 41%. Through 24 weeks of therapy, 11% of patients assigned to zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Antiviral response beyond week 24 is not interpretable because the majority of patients discontinued or changed their antiretroviral therapy.

NRTI-Experienced Adults: PROAB3006, a randomized, open-label multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus NRTIs versus indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80%

male, with a median CD4 cell count of 404 cells/mm^3 (range 9 to 1706 cells/mm^3) and a median plasma HIV-1 RNA level of 3.93 $\log_{10}$ copies/mL (range 2.60 to 7.01 $\log_{10}$ copies/mL) at baseline. Through 48 weeks of therapy, the median CD4 cell count increase from baseline in the amprenavir group was significantly lower than in the indinavir group, 97 cells/mm^3 versus 144 cells/mm^3, respectively. There was also a significant difference in the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 48 weeks (see Figure 1 and Table 5).

Figure 1: Virologic Response Through Week 48, PROAB3006*,†



HIV-1 RNA status and reasons for discontinuation of randomized treatment at 48 weeks are summarized (Table 5).

Table 5: Outcomes of Randomized Treatment Through Week 48 (PROAB3006)

Outcome	AGENERASE (n = 254)	Indinavir (n = 250)
HIV RNA <400 copies/mL*	30%	49%
HIV RNA ≥400 copies/mL†,‡	38%	26%
Discontinued due to adverse events*‡	16%	12%
Discontinued due to other reasons‡,§	16%	13%

*Corresponds to rates at Week 48 in Figure 1.

†Virological failures at or before Week 48.

‡Considered to be treatment failure in the analysis.

§Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations, non-compliance, pregnancy, never treated, and other reasons.

CONTRAINDICATIONS: Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see WARNINGS and PRECAUTIONS).

Coadministration of AGENERASE is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 6.

Table 6: Drugs That are Contraindicated with AGENERASE

Drug Class	Drugs Within Class That Are CONTRAINDICATED with AGENERASE
Alcohol-dependence treatment	Disulfiram
Antibiotic	Metronidazole
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hyponotics	Midazolam, triazolam

AGENERASE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

WARNINGS: ALERT: Find out about medicines that should not be taken with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

If patients require treatment with AGENERASE Oral Solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with AGENERASE (see CONTRAINDICATIONS).

Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of amprenavir by about 90%.

Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including AGENERASE, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.

Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS: Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil).

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with AGENERASE (see ADVERSE REACTIONS).

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

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

PRECAUTIONS:

General: AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY: Pediatric Patients and CONTRAINDICATIONS).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. AGENERASE should be used with caution in patients with a known sulfonamide allergy.

AGENERASE is principally metabolized by the liver; therefore caution should be exercised when administering this drug to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

Formulations of AGENERASE provide high daily doses of vitamin E (see Information for Patients, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

Patients with Hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional

factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors. It is also unknown what effect previous treatment with other protease inhibitors will have on the activity of amprenavir (see MICROBIOLOGY).

Information for Patients: A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with AGENERASE.** A Patient Package Insert (PPI) for AGENERASE Oral Solution is available for patient information.

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole. AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Patients treated with AGENERASE Capsules should be cautioned against switching to AGENERASE Oral Solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Patients should be informed that AGENERASE is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of AGENERASE (amprenavir) are unknown at

this time. Patients should be told that there are currently no data demonstrating that therapy with AGENERASE can reduce the risk of transmitting HIV to others through sexual contact.

Patients should remain under the care of a physician while using AGENERASE. Patients should be advised to take AGENERASE every day as prescribed. AGENERASE must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.

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

Patients taking antacids (or the buffered formulation of didanosine) should take AGENERASE at least 1 hour before or after antacid (or the buffered formulation of didanosine) use.

Patients should be advised that drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients receiving hormonal contraceptives should be instructed that alternate contraceptive measures should be used during therapy with AGENERASE.

High-fat meals may decrease the absorption of AGENERASE and should be avoided. AGENERASE may be taken with meals of normal fat content.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Drug Interactions.

AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

425 **Table 7: Drugs That Should Not Be Coadministered with AGENERASE**

Drug Class/Drug Name	Clinical Comment
Alcohol-dependence treatment: Disulfiram	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the exipient, propylene glycol, in AGENERASE Oral Solution.
Antibiotic: Metronidazole	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the exipient, propylene glycol, in AGENERASE Oral Solution.
Antihistamines: Astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: Rifampin	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
HMG Co-Reductase Inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

426

427 **Table 8: Established and Other Potentially Significant Drug Interactions:**

428 **Alteration in Dose or Regimen May be Recommended Based on Drug Interaction**

429 **Studies or Predicted Interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: Efavirenz, nevirapine	↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
Non-nucleoside Reverse		

Transcriptase Inhibitor: Delavirdine	↑Amprenavir	Appropriate doses of the combination with respect to safety and efficacy have not been established
Nucleoside Reverse Transcriptase Inhibitor: Didanosine (buffered formulation only)	↓Amprenavir	Take AGENERASE at least 1 hour before or after the buffered formulation of didanosine.
HIV-Protease Inhibitors: Indinavir*, lopinavir/ritonavir, nelfinavir*, ritonavir	↑Amprenavir Amprenavir's effect on other protease inhibitors is not well established.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-Protease Inhibitor: Saquinavir*	↓Amprenavir Amprenavir's effect on saquinavir is not well established.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Other Agents		
Antacids	↓Amprenavir	Take AGENERASE at least 1 hour before or after antacids.
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	↑Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with AGENERASE, if available.
Antiarrhythmic: Bepridil	↑Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antifungals: Ketoconazole, itraconazole	↑Ketoconazole ↑Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.
Antimycobacterial: Rifabutin*	↑Rifabutin and rifabutin metabolite	A dosage reduction of rifabutin to at least half the recommended dose is required when AGENERASE and rifabutin are coadministered.* A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.
Benzodiazepines:		

Alprazolam, clorazepate, diazepam, flurazepam	↑Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium Channel Blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Erectile Dysfunction Agent: Sildenafil	↑Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: Atorvastatin, cerivastatin	↑Atorvastatin, ↑Cerivastatin	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with AGENERASE.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.
Oral Contraceptive: Ethinyl estradiol	Effect on ethinyl estradiol is not known.	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and AGENERASE are coadministered.
Tricyclic Antidepressants: Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with AGENERASE.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

Carcinogenesis and Mutagenesis: Long-term carcinogenicity studies of amprenavir in rodents are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Fertility: The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

Pregnancy and Reproduction: AGENERASE Oral Solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content. Therefore, if AGENERASE is used in pregnant women, the AGENERASE Capsules formulation should be used (see complete prescribing information for AGENERASE Capsules).

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

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

Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient propylene glycol (see CONTRAINDICATIONS and WARNINGS). Alcohol dehydrogenase (ADH), which metabolizes propylene glycol, is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

Two hundred fifty-one patients aged 4 and above have received amprenavir as single or multiple doses in studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

Geriatric Use: Clinical studies of AGENERASE 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.

ADVERSE REACTIONS: In clinical studies, adverse events leading to amprenavir discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort), which were mild to moderate in severity.

Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001 and PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a median duration of 10 days. Skin rashes led to amprenavir discontinuation in approximately 3% of patients. In some patients with mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence.

Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson syndrome, occurred in approximately 1% of recipients of AGENERASE (see WARNINGS). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Table 9: Selected Clinical Adverse Events of All Grades Reported in >5% of Adult Patients

Adverse Event	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
	AGENERASE*/ Lamivudine/ Zidovudine (n = 113)	Lamivudine/ Zidovudine (n = 109)	AGENERASE*/ NRTI (n = 245)	Indinavir/NRTI (n = 241)
Digestive				
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
Skin				
Rash	27%	6%	20%	15%
Nervous				
Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
Psychiatric				
Depressive or mood disorders	16%	4%	9%	13%

*AGENERASE Capsules

Among amprenavir-treated patients in Phase 3 studies, 2 patients developed de novo diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

Table 10: Selected Laboratory Abnormalities of All Grades Reported in ≥5% of Adult Patients

Laboratory Abnormality (non-fasting specimens)	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
	AGENERASE*/ Lamivudine/ Zidovudine (n = 111)	Lamivudine/ Zidovudine (n = 108)	AGENERASE*/ NRTI (n = 237)	Indinavir/NRTI (n =239)
Hyperglycemia (>116 mg/dL)	45%	31%	53%	58%
Hypertriglyceridemia (>213 mg/dL)	41%	27%	56%	52%
Hypercholesterolemia (>283 mg/dL)	7%	3%	13%	15%

*AGENERASE Capsules

In studies PROAB3001 and PROAB3006, no increased frequency of Grade 3 or 4 AST, ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in pediatric patients.

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

AGENERASE Oral Solution contains large amounts of propylene glycol. In the event of overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene glycol can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION: AGENERASE may be taken with or without food; however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see CLINICAL PHARMACOLOGY: Effects of Food on Oral Absorption).

519 **Adult and pediatric patients should be advised not to take supplemental vitamin E**
520 **since the vitamin E content of AGENERASE Oral Solution exceeds the Reference**
521 **Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).**
522 The recommended dose of AGENERASE Oral Solution based on body weight and age
523 is shown in Table 10. **Consideration should be given to switching patients from**
524 **AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to**
525 **take the capsule formulation (see WARNINGS).**
526
527 **Table 10: Recommended Dosages of AGENERASE Oral Solution**

Age/Weight Criteria	Dose	
	b.i.d.	t.i.d.
4 - 12 years or 13 - 16 years and <50 kg	22.5 mg/kg (1.5 mL/kg) (maximum dose 2800 mg per day)	17 mg/kg (1.1 mL/kg) (maximum dose 2800 mg per day)
13 - 16 years and ≥50 kg or >16 years	1400 mg	NA

528
529 **Patients with Hepatic Impairment:** AGENERASE Oral Solution is contraindicated in
530 patients with hepatic failure (see CONTRAINDICATIONS).
531 Patients with hepatic impairment are at increased risk of propylene glycol-associated
532 adverse events (see WARNINGS). AGENERASE Oral Solution should be used with
533 caution in patients with hepatic impairment. Based on a study with AGENERASE
534 Capsules, adult patients with a Child-Pugh score ranging from 5 to 8 should receive a
535 reduced dose of AGENERASE Oral Solution of 513 mg (34 mL) twice daily, and adult
536 patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of
537 AGENERASE Oral Solution of 342 mg (23 mL) twice daily (see CLINICAL
538 PHARMACOLOGY: Hepatic Insufficiency).
539 AGENERASE Oral Solution has not been studied in children with hepatic impairment.
540 **Renal Insufficiency:** AGENERASE Oral Solution is contraindicated in patients with renal
541 failure (see CONTRAINDICATIONS).

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. AGENERASE Oral Solution should be used with caution in patients with renal impairment (see WARNINGS).

AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED:

AGENERASE Oral Solution, a clear, pale yellow to yellow, grape bubblegum-peppermint-flavored liquid, contains 15 mg of amprenavir in each 1 mL.

Bottles of 240 mL with child-resistant closures (NDC 0173-0687-00). This product does not require reconstitution.

Store at controlled room temperature of 25°C (77°F) (see USP).

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Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

VERTEX
Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

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US Patent Nos. 5,585,397; 5,723,490; and 5,646,180

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Date of Issue RL no. –

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

AGENERASE® (amprenavir) Oral Solution

ALERT: Find out about medicines that should not be taken with AGENERASE. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH AGENERASE."

Please read this information before you start taking AGENERASE (pronounced ah-GEN-er-ase) Oral Solution, and re-read it each time you receive your prescription, just in case something has changed. Remember that this information does not take the place of careful discussions with your doctor when you start this medication and at checkups. You should not change or stop your anti-HIV treatment without first talking with your doctor. **You should tell your doctor about any drug you are taking or planning to take because taking AGENERASE Oral Solution with some medications can result in serious or life-threatening problems.**

What is AGENERASE Oral Solution?

AGENERASE Oral Solution is a medication used to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome). AGENERASE Oral Solution is taken by mouth as an oral solution. It belongs to a class of anti-HIV medicines called protease inhibitors.

What is the Important Safety Information on AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used in infants and children below the age of 4 years, pregnant women, patients with liver or kidney failure, and patients receiving disulfiram (ANTABUSE®) or metronidazole (FLAGYL®).

AGENERASE Oral Solution contains a large amount of propylene glycol, a liquid needed to dissolve amprenavir. Because of the possible side effects of the large amount of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE

Capsules or other protease inhibitor formulations are not options. You should not switch from AGENERASE Capsules to AGENERASE Oral Solution without talking to your doctor.

If you are a woman or an Asian, Eskimo, or Native American, or if you have liver or kidney disease, you may be at increased risk of side effects from the large amount of propylene glycol in AGENERASE Oral Solution.

How does AGENERASE Oral Solution work?

AGENERASE Oral Solution is used only in combination with other anti-HIV medicines. When used in combination therapy, AGENERASE Oral Solution may help lower the amount of HIV found in your blood, raise CD4 (T) cell count, and keep your immune system as healthy as possible so that it can help fight infection. However, AGENERASE Oral Solution does not have these effects in all patients.

What are the side effects of AGENERASE Oral Solution?

Common side effects of AGENERASE Oral Solution are nausea, vomiting, diarrhea, rash, and a tingling sensation around the mouth. Severe or life-threatening rash has been reported.

Possible side effects from the large amount of propylene glycol in AGENERASE Oral Solution include seizures, drowsiness, fast heart rate, and kidney and blood abnormalities.

Contact your doctor if you have nausea, vomiting, diarrhea, or rash. Your doctor may be able to help you manage these symptoms. Your doctor will advise you whether your symptoms can be managed on therapy or whether AGENERASE Oral Solution should be stopped.

This list of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with AGENERASE Oral Solution. Talk to your doctor promptly about any side effects you have.

How should I take AGENERASE Oral Solution?

Take AGENERASE Oral Solution exactly as your doctor prescribes it. AGENERASE Oral Solution can be taken with or without food. However, you should not take AGENERASE with a high-fat meal because this could reduce the effectiveness of AGENERASE Oral Solution.

What should I do if I miss a dose of AGENERASE Oral Solution?

To help make sure that your anti-HIV therapy is as effective as possible, be very careful to take all of your medication exactly as your doctor prescribed it and do not skip any doses.

If you miss a dose of AGENERASE Oral Solution by more than 4 hours, wait and take the next dose at the regularly scheduled time. However, if you miss a dose by fewer than 4 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of AGENERASE Oral Solution at any one time.

When your supply of AGENERASE Oral Solution or other anti-HIV drugs starts to run low, arrange to get more from your doctor or pharmacy. It is very important that you take anti-HIV drugs as prescribed by your doctor because the amount of virus in your blood may increase if one or more of the drugs is stopped, even for a short time.

Can AGENERASE Oral Solution be taken with other medications?

Protease inhibitors, including AGENERASE, may interact with other drugs, including those you take without a prescription. Before you take AGENERASE, tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

MEDICINES YOU SHOULD NOT TAKE WITH AGENERASE

- **AGENERASE Oral Solution should <u>not</u> be taken with ANTABUSE (disulfiram) or FLAGYL (metronidazole).**

- Drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution because it may increase side effects related to propylene glycol content.

- **You <u>should not take</u> any of the following medications with AGENERASE Oral Solution because serious or life-threatening problems could occur.***

HALCION® (triazolam)	PROPULSID® (cisapride)
HISMANAL® (astemizole)	VERSED® (midazolam)
Ergot medications (CAFERGOT® and others)	VASCOR® (bepridil)
ORAP® (pimozide)	SELDANE® (terfenadine)

- **You should also not take rifampin** with AGENERASE Oral Solution because this drug reduces the effectiveness of AGENERASE. Rifampin is also known as: RIFADIN®, RIFAMATE®, RIFATER®, and RIMACTANE®.

- Taking AGENERASE with St. John's Wort (hypericum perforatum, a nonprescription herbal product) or products containing St. John's Wort is <u>not</u> recommended. Talk with your doctor if you are taking or are planning to take St. John's Wort because St. John's Wort may reduce the effect of AGENERASE.

- It is not recommended that you take AGENERASE with the cholesterol-lowering drugs MEVACOR® (lovastatin) or ZOCOR® (simvastatin) because of the possible drug interactions. There is also an increased risk of drug interactions between AGENERASE and LIPITOR® (atorvastatin), and BAYCOL® (cerivastatin). Talk to your doctor if you are taking or are planning to take these or other drugs for lowering cholesterol.

Medicines That Require Dose Adjustments or Special Attention From Your Doctor

- **Serious and/or life-threatening drug interactions can also occur if you take AGENERASE Oral Solution with any of the following drugs.*** If you need to take any of these drugs, your doctor may <u>closely monitor</u> the amount of drug in your blood to minimize potential problems.

CORDARONE® (amiodarone)

Phenobarbital

TEGRETOL®, CARBATROL® (carbamazepine)

DILANTIN® (phenytoin)

Lidocaine

COUMADIN® (warfarin)

(quinidine) QUINAGLUTE®, CARDIOQUIN®, QUINIDEX®

Antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine), PAMELOR® (nortriptyline), TOFRANIL® (imipramine)

- Tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

- Before you take VIAGRA® (sildenafil) with AGENERASE Oral Solution, talk to your doctor about possible drug interactions and side effects. If you take VIAGRA and AGENERASE Oral Solution together, you may be at increased risk of side effects of VIAGRA such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should seek immediate medical assistance to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you use birth control pills, talk to your doctor about choosing a different type of contraceptive, since AGENERASE Oral Solution may reduce the effectiveness of some birth control pills.

- Because AGENERASE Oral Solution contains large amounts of vitamin E, you should not take additional vitamin E while taking AGENERASE Oral Solution.

-

- **Special considerations:***

If you take AGENERASE Oral Solution with MYCOBUTIN® (rifabutin), your doctor will lower the dose of MYCOBUTIN.

If you take AGENERASE Oral Solution with VIDEX® (didanosine, ddI)(buffered formulation), take them at least 1 hour apart.

If you take AGENERASE Oral Solution with antacids, take them at least 1 hour apart.

Does AGENERASE Oral Solution cure HIV infection or AIDS?

AGENERASE Oral Solution does not cure HIV infection or AIDS. At this time we do not know if AGENERASE will help you live longer or have fewer of the medical problems (opportunistic infections) that are associated with HIV infection or AIDS. Because of this, you must be sure to be seen regularly by your healthcare professional.

Does AGENERASE Oral Solution reduce the risk of passing HIV to others?

No. AGENERASE Oral Solution, as well as other anti-HIV medications, has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

Who should not take AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used in infants and children below 4 years of age, pregnant women, patients with liver or kidney failure, or patients on disulfiram (ANTABUSE) or metronidazole (FLAGYL).

Do not take AGENERASE Oral Solution if you have had a serious allergic reaction to AGENERASE Oral Solution or any of its ingredients. If you have liver disease, your dosage of AGENERASE Oral Solution may have to be adjusted.

If you are allergic to sulfa drugs, you should inform your doctor.

Can children take AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used in infants and children below 4 years of age.

Children from 4 to 12 years of age can take AGENERASE Oral Solution. Your doctor will tell you if the oral solution or capsule is best for your child. Your child's doctor will decide the right dose based on your child's weight and age.

Can pregnant women and nursing mothers take AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used by pregnant women. Talk to your doctor if you are pregnant or if you become pregnant while taking AGENERASE Oral Solution.

Mothers with HIV should not breastfeed their infants because HIV in the breast milk can infect the infant.

What other medical conditions should I discuss with my doctor?

Talk to your doctor if you are pregnant or if you become pregnant while you are taking AGENERASE Oral Solution.

Also talk to your doctor if you have hemophilia or problems with your liver or kidneys.

How should I store AGENERASE Oral Solution?

AGENERASE Oral Solution should be stored at room temperature and should not be refrigerated.

Other information:

This medication is prescribed for a particular condition. Do not use it for any other condition or give it to anybody else. Keep AGENERASE Oral Solution and all medicines out of the reach of children.

Ask a healthcare professional any questions you may have about AGENERASE Oral Solution.

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