PRODUCT INFORMATION

AGENERASE®

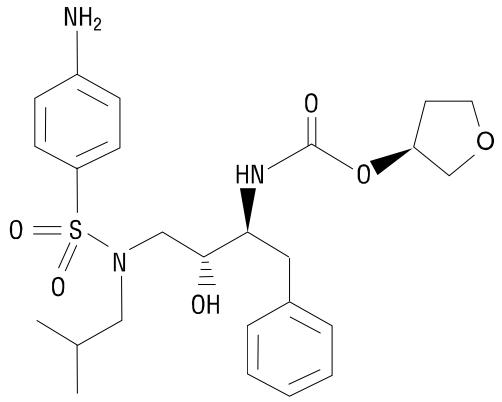
(amprenavir)

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)
Ethinyl estradiol/ Norethindrone	0.035 mg/1 mg for 1 cycle	1200 mg b.i.d. for 28 days	10	⇔ (↓20 to ↑3)	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole	400 mg single dose	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)
Ritonavir	100 mg b.i.d. for 2 to 4 weeks	600 mg b.i.d.	18	↓30† (↓44 to ↓14)	↑64† (↑37 to ↑97)	↑508† (↑394 to ↑649)
Ritonavir	200 mg q.d. for 2 to 4 weeks	1200 mg q.d.	12	⇔† (↓17 to ↑30)	↑62† (↑35 to ↑94)	↑319† (↑190 to ↑508)

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.

†Compared to amprenavir 1200 mg b.i.d. in the same patients.

↑ = 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)
Ethinyl estradiol	0.035 mg for 1 cycle	1200 mg b.i.d. for 28 days	10	⇔ (↓25 to ↑15)	⇔ (↓14 to ↑38)	↑32 (↓3 to ↑79)
Norethindrone	1.0 mg for 1 cycle	1200 mg b.i.d. for 28 days	10	⇔ (↓20 to ↑18)	↑18 ↑1 to ↑38	↑45 ↑13 to ↑88
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
Methadone	44 to 100 mg q.d. for >30 days	1200 mg b.i.d. for 10 days	16	R-Methadone (active)		
				↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
				S-Methadone (inactive)		
				↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
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.

Methadone: Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

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).

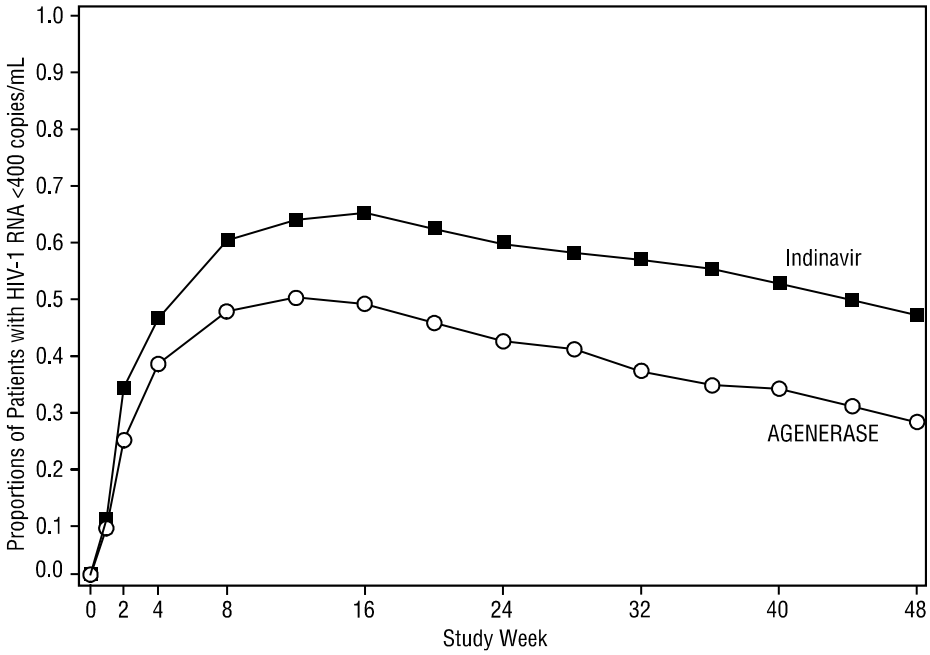
There are no data on response to therapy with AGENERASE in protease inhibitor-experienced patients.

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 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*,†



*Roche AMPLICOR HIV-1 MONITOR assay.
†Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

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: 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**
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

If AGENERASE is coadministered with ritonavir, the antiarrhythmic agents flecainide and propafenone are also contraindicated.

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). 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. AGENERASE, when used alone and in combination with low-dose ritonavir, has been associated with elevations of SGOT (AST) and SGPT (ALT) in some patients. Caution should be exercised when administering AGENERASE to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION). Appropriate laboratory testing should be conducted prior to initiating therapy with AGENERASE and at periodic intervals during treatment.

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, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations: Treatment with AGENERASE alone or in combination with ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiation of therapy with AGENERASE and at periodic intervals during treatment. Lipid disorders should be managed as clinically appropriate. See PRECAUTIONS Table 8: Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with AGENERASE and HMG-CoA reductase inhibitors.

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 healthcare 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 or 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 taking AGENERASE should be instructed **not** to use hormonal contraceptives because some birth control pills (those containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Therefore, patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures 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 antiretroviral therapy 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).

Laboratory Tests: The combination of AGENERASE and low-dose ritonavir has been associated with elevations of cholesterol and triglycerides, SGOT (AST), and SGPT (ALT) in some patients. Appropriate laboratory testing should be considered prior to initiating combination therapy with AGENERASE and ritonavir and at periodic intervals or if any clinical signs or symptoms of hyperlipidemia or elevated liver function tests occur during therapy. For comprehensive information concerning laboratory test alterations associated with ritonavir, physicians should refer to the complete prescribing information for NORVIR® (ritonavir).

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).

Table 7: Drugs That Should Not Be Coadministered with AGENERASE

Drug Class/Drug Name	Clinical Comment
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.
Oral contraceptives: Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to AGENERASE. Alternative methods of non-hormonal contraception are recommended.
Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 8: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction 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*	↑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: Ritonavir*	↑Amprenavir	The dose of amprenavir should be reduced when used in combination with ritonavir (see Dosage and Administration). Also, see the full prescribing information for NORVIR® for additional drug interaction information.
	↓Amprenavir	

HIV-Protease Inhibitor: Saquinavir*	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.
	↑Rifabutin and	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

Antimycobacterial: Rifabutin*	rifabutin metabolite	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	↑Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with AGENERASE.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑Immunosup-pressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.

	↓Amprenavir	AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered.
Narcotic analgesics: Methadone*	↓Methadone	Dosage of methadone may need to be increased when coadministered with AGENERASE.
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

	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
Adverse Event	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

	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
Laboratory Abnormality (non-fasting specimens)	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.

Concomitant Therapy with Ritonavir:

Table 11: Selected Clinical Adverse Events of all Grades Reported in ≥5% of Adult Patients in Ongoing, Open-Label Clinical Trials of AGENERASE in Combination with Ritonavir

	AGENERASE 1200 mg plus Ritonavir 200 mg q.d.* (n = 101)	AGENERASE 600 mg plus Ritonavir 100 mg b.i.d.† (n = 215)
Diarrhea/loose stools	25%	7%
Nausea	23%	7%
Vomiting	10%	4%
Abdominal symptoms	13%	3%
Headache	15%	3%
Paresthesias	8%	2%
Rash	9%	2%
Fatigue	5%	4%

*Data from 2 ongoing, open-label studies in treatment-naive patients also receiving abacavir/lamivudine.

†Data from 3 ongoing, open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

Treatment with AGENERASE in combination with ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides (see PRECAUTIONS Lipid Elevations and Laboratory Tests).

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.

Concomitant Therapy: If AGENERASE and ritonavir are used in combination, the recommended dosage regimens are: AGENERASE 1200 mg with ritonavir 200 mg once daily or AGENERASE 600 mg with ritonavir 100 mg twice daily.

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

GlaxoSmithKline

Research Triangle Park, NC 27709

Licensed from

Vertex Pharmaceuticals Incorporated

Cambridge, MA 02139

AGENERASE is a registered trademark of the GlaxoSmithKline group of companies.

Date of Issue

RL-

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. Read the section: "What important information should I know about taking AGENERASE with other medicines?"

Read this information carefully before you start taking AGENERASE (ah-GEN-er-ase). Read the information each time you get more medicine. There may be new information. This information does not take the place of talks with your healthcare provider when you start this medicine and at checkups.

What is the most important information I should know about AGENERASE?

AGENERASE can cause serious and life-threatening side effects if you take it with certain other medicines. For information about these medicines, see the section "What important information should I know about taking AGENERASE with other medicines?"

What is AGENERASE?

AGENERASE is a medicine you take by mouth to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome.) AGENERASE belongs to a class of anti-HIV medicines called protease inhibitors.

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

AGENERASE does not cure HIV infection or AIDS. We do not know if AGENERASE will help you live longer or have fewer of the medical problems (opportunistic infections) that people get with HIV or AIDS. Therefore, be sure to see your healthcare provider regularly. The long-term effects of AGENERASE are not known.

AGENERASE has not been shown to reduce the risk of passing HIV to others through sexual contact or blood. Continue to practice safe sex and do not use or share dirty needles.

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

AGENERASE has not been studied in people who have taken anti-HIV medicine combinations before that included a protease inhibitor.

Who should not take AGENERASE?

Do not take AGENERASE Capsules if

- you are taking certain medicines. Read the section entitled **"What important information should I know about taking AGENERASE with other medicines?"**
- you have had an allergic reaction to AGENERASE or any of its ingredients.

Children younger than age 4 should not take AGENERASE Capsules or AGENERASE Oral Solution.

Tell your healthcare provider if

- you are pregnant, AGENERASE Capsules may not be right for you.
- you are breastfeeding. Your baby can get HIV from your milk. Also, AGENERASE can pass through your milk and harm the baby.

Tell your healthcare provider about all your medical conditions. AGENERASE may not be right for you, or you may need a dosage change in AGENERASE. Be sure to tell your healthcare provider if you

- have liver or kidney problems.
- have hemophilia.
- are allergic to sulfa medicines. AGENERASE may cause problems for you.

What important information should I know about taking AGENERASE with other medicines?

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and supplements. **Some of them may cause dangerous and life-threatening side effects** if you take them during treatment with AGENERASE. For other medicines, you may need to change your dose to avoid problems.

- If you are on methadone therapy, talk to your doctor about possible interactions.

Do NOT take the following medicines* with AGENERASE. You could develop serious or life-threatening problems.

- HALCION® (triazolam; used for insomnia)
- CAFERGOT® and other ergot medicines (used for migraine headaches)
- PROPULSID® (cisapride, used for certain stomach problems)
- VERSED® (midazolam; used for sedation)
- ORAP® (pimozide; used for Tourette's disorder)

You will need to be monitored with regular blood tests if you take the following medicines* with AGENERASE.

- CORDARONE® (amiodarone; used for certain abnormal heart rhythms)
- Quinidine (used for certain abnormal heart rhythms)
- COUMADIN® (warfarin; used for blood thinning)
- Lidocaine (used for certain abnormal heart rhythms)

- ELAVIL® (amitiptyline), TOFRANIL® (imipramine) (tricyclic antidepressants)
- SANDIMMUNE® or NEORAL® (cyclosporine), PROGRAF® (tacrolimus), RAPAMUNE® (rapamycin or sirolimus) (immunosuppressants)

You will need to have your dose adjusted if you take the following medicines* with AGENERASE.

- MYCOBUTIN® (rifabutin; used to prevent *Mycobacterium* avium complex [MAC])
- NORVIR® (ritonavir; used to treat HIV infection)
- VIAGRA® (sildenafil; used for impotence). You may get increased side effects such as low blood pressure, changes in vision, or erections that last more than 4 hours. If an erection lasts more than 4 hours, get medical help right away.

The following medicines* may cause serious problems if you take them with AGENERASE. Tell your healthcare provider if you are taking any of these medicines.

- St. John's wort (hypericum perforatum) or products containing St. John's wort
- VASCOR® (bepridil; used for chronic stable angina)
- RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE® (rifampin, used for tuberculosis)
- MEVACOR® (lovastatin), ZOCOR® (simvastatin), and LIPITOR® (atorvastatin) (cholesterol-lowering medicines)
- Phenobarbital (used for seizures)
- TEGRETOL®, CARBATROL® (carbamazepine; used for seizures and trigeminal neuralgia)
- DILANTIN® (phenytoin; used for seizures)
- DECADRON® (dexamethasone, used to reduce inflammation)
- Hormonal contraceptives (e.g., birth control pills) because the effectiveness of one or both drugs may be decreased. Talk to your doctor about choosing a different type of contraceptive.
- Certain other anti-HIV medicines
- Vitamin E. AGENERASE contains high daily doses of vitamin E that could interfere with medicines that help you stop bleeding.

This list is not complete. Be sure to tell your healthcare provider about <u>all</u> the medicines you

take.

How should I take AGENERASE?

- Take AGENERASE Capsules every day exactly as your healthcare provider has prescribed it**, so it will be as effective as possible**. Your healthcare provider will decide the right dose for you.
- If you miss a dose **by more than 4 hours, wait and take the next dose at the regular time. However, if you miss a dose by fewer than 4 hours, take your missed dose right away. Then take your next dose at the regular time.**
- **Do not take more or less than your prescribed dose of AGENERASE Capsules at any one time.** Do not change your dose or stop taking AGENERASE without talking with your healthcare provider.
- You can take AGENERASE Capsules with or without food**. However, do not take AGENERASE with a high–fat meal. This could reduce the effectiveness of the medicine.**
- If you take AGENERASE with the **buffered form of VIDEX® (didanosine, ddI), take them at least 1 hour apart.**
- If you take AGENERASE Capsules with antacids**, take them at least 1 hour apart.**
- When your supply of AGENERASE or other anti-HIV medicine starts to run low**, arrange to get more from your healthcare provider or pharmacy. The amount of virus in your blood may increase if one or more of the drugs are stopped, even for a short time.**
- Stay under the care of a healthcare provider while using AGENERASE.

What should I avoid while taking AGENERASE?

Do not

- **switch from AGENERASE Capsules to AGENERASE Oral Solution without talking to your healthcare provider. You may get increased side effects if you switch.**
- take vitamin E while taking AGENERASE. It contains large amounts of vitamin E.
- take AGENERASE with a high-fat meal. It could reduce the effectiveness of the medicine.

What are the possible side effects of AGENERASE?

AGENERASE can cause a severe or life-threatening rash. Call your healthcare provider right

away if you have a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether AGENERASE should be stopped.

Common side effects of AGENERASE are nausea, vomiting, diarrhea, rash, and a tingling feeling, especially around the mouth, and change in taste. These are usually mild to moderate. Depression and mood problems have also been reported in patients taking AGENERASE.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Other side effects include high blood sugar or diabetes, diabetes complications, high cholesterol, or high triglycerides.

This list of side effects is not complete. Your healthcare provider or pharmacist can give you a more complete list of possible side effects. Talk with your healthcare provider about any concerns about the way you are feeling while you are taking AGENERASE.

How should I store AGENERASE Capsules?
AGENERASE Capsules should be stored at room temperature and should not be refrigerated.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use AGENERASE for a condition for which it was not prescribed. Do not give AGENERASE to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about AGENERASE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AGENERASE that is written for health professionals.

GlaxoSmithKline.
Research Triangle Park, NC 27709

Licensed from

Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

Date of Issue

RL-

PRODUCT INFORMATION

AGENERASE®

(amprenavir)

Oral Solution

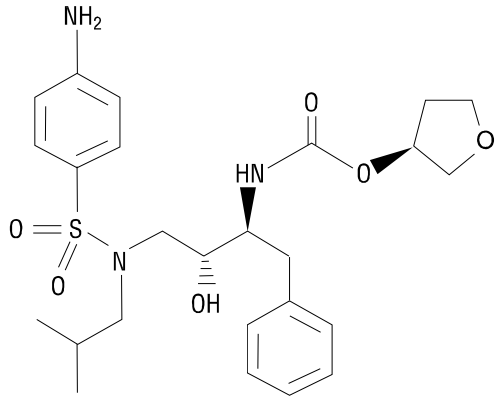
PATIENT INFORMATION INCLUDED

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_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.

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.

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

175 **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)
Ethinyl estradiol/ Norethindrone	0.035 mg/1 mg for 1 cycle	1200 mg b.i.d. for 28 days	10	⇔ (↓20 to ↑3)	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole	400 mg single dose	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)
Ritonavir	100 mg b.i.d. for 2 to 4 weeks	600 mg b.i.d.	18	↓30† (↓44 to ↓14)	↑64† (↑37 to ↑97)	↑508† (↑394 to ↑649)
Ritonavir	200 mg q.d. for 2 to 4 weeks	1200 mg q.d.	12	⇔† (↓17 to ↑30)	↑62† (↑35 to ↑94)	↑319† (↑190 to ↑508)

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.

†Compared to amprenavir capsules 1200 mg b.i.d. in the same patients.

↑ = 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)
Ethinyl estradiol	0.035 mg for 1 cycle	1200 mg b.i.d. for 28 days	10	⇔ (↓25 to ↑15)	⇔ (↓14 to ↑38)	↑32 (↓3 to ↑79)
Norethindrone	1.0 mg for 1 cycle	1200 mg b.i.d. for 28 days	10	⇔ (↓20 to ↑18)	↑18 ↑1 to ↑38	↑45 ↑13 to ↑88
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
Methadone	44 to 100 mg q.d. for >30 days	1200 mg b.i.d. for 10 days	16	R-Methadone (active)		
				↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
				S-Methadone (inactive)		
				↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
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: Concurrent use of AGENERASE Oral Solution and NORVIR® (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination**.** This combination has not been studied in pediatric patients.

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.

Methadone: Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

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**

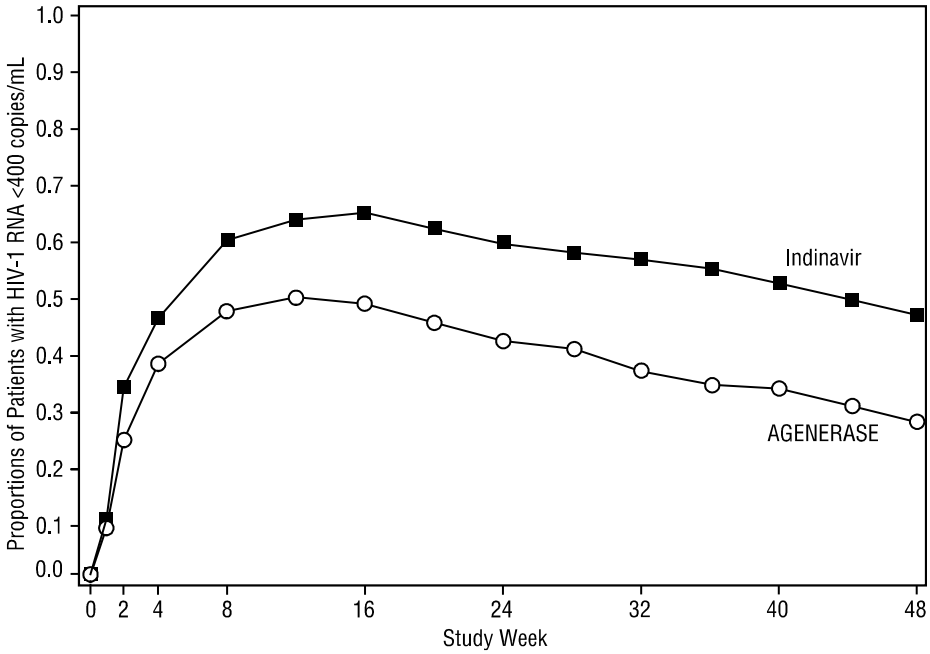
inhibitor-experienced patients.

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*,†



*Roche AMPLICOR HIV-1 MONITOR assay.
†Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

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 Oral Solution

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

If AGENERASE Capsules are coadministered with ritonavir capsules, the antiarrhythmic agents flecainide and propafenone are also contraindicated.

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.

Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination.

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). 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. AGENERASE, when used alone and in combination with low-dose ritonavir, has been associated with elevations of SGOT (AST) and SGPT (ALT) in some patients. Caution should be exercised when administering AGENERASE to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION). Appropriate laboratory testing should be conducted prior to initiating therapy with AGENERASE and at periodic intervals during treatment.

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, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations: Treatment with AGENERASE alone or in combination with ritonavir capsules has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiation of therapy with AGENERASE and at periodic intervals during treatment. Lipid disorders should be managed as clinically appropriate. See PRECAUTIONS Table 8: Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with AGENERASE and HMG-CoA reductase inhibitors.

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 healthcare 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 or 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 taking AGENERASE should be instructed **not** to use hormonal contraceptives because some birth control pills (those containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Therefore, patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures 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 antiretroviral therapy 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).

Laboratory Tests: The combination of AGENERASE and low-dose ritonavir has been associated with elevations of cholesterol and triglycerides, SGOT (AST), and SGPT (ALT) in some patients. Appropriate laboratory testing should be considered prior to initiating combination therapy with AGENERASE and ritonavir capsules and at periodic intervals or if any clinical signs or symptoms of hyperlipidemia or elevated liver function tests occur during therapy. For comprehensive information concerning laboratory test alterations associated with ritonavir, physicians should refer to the complete prescribing information for NORVIR (ritonavir)

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.

Table 7: Drugs That Should Not Be Coadministered with AGENERASE Oral Solution

Drug Class/Drug Name	Clinical Comment
Alcohol-dependence treatment: Disulfiram	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the excipient, propylene glycol, in AGENERASE Oral Solution.
Antibiotic: Metronidazole	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the excipient, propylene glycol, in AGENERASE Oral Solution.
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.
HIV-Protease Inhibitor: Ritonavir oral solution	Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination**.**
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.
Oral contraceptives: Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to AGENERASE. Alternative methods of non-hormonal contraception are recommended.

Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 8: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction 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*	↑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.
		The dose of amprenavir should be reduced when used in combination with ritonavir capsules (see

HIV-Protease Inhibitor: Ritonavir Capsules*	↑Amprenavir	Dosage and Administration). Also, see the full prescribing information for NORVIR for additional drug interaction information. Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination**.**
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.
		Increase monitoring for adverse events due to

Antifungals: Ketoconazole, itraconazole	↑Ketoconazole ↑Itraconazole	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	↑Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with AGENERASE.

Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑Immunosup-pressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.
	↓Amprenavir	AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered.
Narcotic analgesics: Methadone*	↓Methadone	Dosage of methadone may need to be increased when coadministered with AGENERASE.
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.

Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination**.** This combination has not been studied 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.

Concomitant Therapy with Ritonavir:

Table 11: Selected Clinical Adverse Events of all Grades Reported in ≥5% of Adult Patients in Ongoing, Open-Label Clinical Trials of AGENERASE Capsules in Combination with Ritonavir Capsules

Adverse Event	AGENERASE 1200 mg plus Ritonavir 200 mg q.d.* (n = 101)	AGENERASE 600 mg plus Ritonavir 100 mg b.i.d.† (n = 215)
Diarrhea/loose stools	25%	7%
Nausea	23%	7%
Vomiting	10%	4%
Abdominal symptoms	13%	3%
Headache	15%	3%
Paresthesias	8%	2%
Rash	9%	2%
Fatigue	5%	4%

*Data from 2 ongoing, open-label studies in treatment-naive patients also receiving abacavir/lamivudine.

†Data from 3 ongoing, open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

Treatment with AGENERASE in combination with ritonavir capsules has resulted in increases in the concentration of total cholesterol and triglycerides (see PRECAUTIONS: Lipid Elevations and Laboratory Tests).

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

The recommended dose of AGENERASE Oral Solution based on body weight and age is shown in Table 12. **Consideration should be given to switching patients from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation (see WARNINGS).**

Table 12: 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

Concomitant Therapy: Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination.

Patients with Hepatic Impairment: AGENERASE Oral Solution is contraindicated in patients with hepatic failure (see CONTRAINDICATIONS).

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. Based on a study with AGENERASE Capsules, adult patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Oral Solution of 513 mg (34 mL) twice daily, and adult patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE Oral Solution of 342 mg (23 mL) twice daily (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency).

AGENERASE Oral Solution has not been studied in children with hepatic impairment.

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

Licensed from

GlaxoSmithKline

Research Triangle Park, NC 27709

VERTEX

Vertex Pharmaceuticals Incorporated

Cambridge, MA 02139

Date of Issue RL-

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 Oral Solution. Read the section: "<u>What important information should I know about taking AGENERASE Oral Solution with other medicines</u>?"

Read this information carefully before you start taking AGENERASE (ah-GEN-er-ase) Oral Solution. Read the information each time you get more medicine. There may be new information. This information does not take the place of talks with your healthcare provider when you start this medicine and at checkups.

<u>What is the most important information I should know about AGENERASE?</u>

AGENERASE can cause serious and life-threatening side effects if you take it with certain other medicines. For information about these medicines, see the section "What important information should I know about taking AGENERASE with other medicines?"

<u>What is AGENERASE Oral Solution?</u>

AGENERASE Oral Solution is a medicine you take by mouth to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome.) AGENERASE belongs to a

class of anti-HIV medicines called protease inhibitors.

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

AGENERASE does not cure HIV infection or AIDS. We do not know if AGENERASE will help you live longer or have fewer of the medical problems (opportunistic infections) that people get with HIV or AIDS. Therefore, be sure to see your healthcare provider regularly. The long-term effects of AGENERASE are not known.

AGENERASE has not been shown to reduce the risk of passing HIV to others through sexual contact or blood. Continue to practice safe sex and do not use or share dirty needles.

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

AGENERASE has not been studied in people who have taken anti-HIV medicine combinations before that included a protease inhibitor.

Who should not take AGENERASE Oral Solution?

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.

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.

Do not take AGENERASE Oral Solution if

- you are taking certain medicines. Read the section entitled **"What important information should I know about taking AGENERASE Oral Solution with other medicines?"**
- you are pregnant.
- you have had an allergic reaction to AGENERASE or any of its ingredients.

Children younger than age 4 should not take AGENERASE Capsules or AGENERASE Oral Solution.

Tell your healthcare provider if

- you are pregnant. Do not use AGENERASE Oral Solution if you are pregnant.
- you are breastfeeding. Your baby can get HIV from your milk. Also, AGENERASE can pass through your milk and harm the baby.

Tell your healthcare provider about all your medical conditions. AGENERASE Oral Solution may not be right for you, or you may need a dosage change in AGENERASE. Be sure to tell your healthcare provider if you

- have liver or kidney problems.
- have hemophilia.
- are allergic to sulfa medicines. AGENERASE may cause problems for you.

What important information should I know about taking AGENERASE Oral Solution with other medicines?

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and supplements. **Some of them may cause dangerous and life-threatening side effects** if you take them during treatment with AGENERASE. For other medicines, you may need to change your dose to avoid problems.

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

Taking AGENERASE Oral Solution and NORVIR (ritonavir) oral solution together is not recommended because this may increase side effects related to propylene glycol and ethanol content.

If you are on methadone therapy, talk to your doctor about possible interactions.

Do NOT take the following medicines* with AGENERASE Oral Solution. You could develop serious or life-threatening problems.

- FLAGYL® (metronidazole, used to treat certain infections)
- ANTABUSE® (disulfiram, used to treat alcohol dependence)
- HALCION® (triazolam; used for insomnia)
- CAFERGOT® and other ergot medicines (used for migraine headaches)
- PROPULSID® (cisapride, used for certain stomach problems)
- VERSED® (midazolam; used for sedation)
- ORAP® (pimozide; used for Tourette's disorder)

You will need to be monitored with regular blood tests if you take the following medicines* with AGENERASE.

- CORDARONE® (amiodarone; used for certain abnormal heart rhythms)
- Quinidine (used for certain abnormal heart rhythms)
- COUMADIN® (warfarin; used for blood thinning)
- Lidocaine (used for certain abnormal heart rhythms)
- ELAVIL® (amitriptyline), TOFRANIL® (imipramine) (tricyclic antidepressants)
- SANDIMMUNE® or NEORAL® (cyclosporine), PROGRAF® (tacrolimus), RAPAMUNE® (rapamycin or sirolimus) (immunosuppressants)

You will need to have your dose adjusted if you take the following medicines* with AGENERASE.

- MYCOBUTIN® (rifabutin; used to prevent *Mycobacterium* avium complex [MAC])
- NORVIR® Capsules (ritonavir capsules; used to treat HIV infection)
- VIAGRA® (sildenafil; used for impotence). You may get increased side effects such as low blood pressure, changes in vision, or erections that last more than 4 hours. If an erection lasts more than 4 hours, get medical help right away.

The following medicines* may cause serious problems if you take them with AGENERASE. Tell your healthcare provider if you are taking any of these medicines.

- St. John's wort (hypericum perforatum) or products containing St. John's wort
- VASCOR® (bepridil; used for chronic stable angina)
- RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE® (rifampin, used for tuberculosis)
- MEVACOR® (lovastatin), ZOCOR® (simvastatin), and LIPITOR® (atorvastatin) (cholesterol-lowering medicines)
- Phenobarbital (used for seizures)
- TEGRETOL®, CARBATROL® (carbamazepine; used for seizures and trigeminal neuralgia)
- DILANTIN® (phenytoin; used for seizures)
- DECADRON® (dexamethasone, used to reduce inflammation)
- Hormonal contraceptives (e.g., birth control pills) because the effectiveness of one or both drugs may be decreased. Talk to your doctor about choosing a different type of contraceptive.
- Certain other anti-HIV medicines
- Vitamin E. AGENERASE contains high daily doses of vitamin E that could interfere with medicines that help you stop bleeding.

This list is not complete. Be sure to tell your healthcare provider about <u>all</u> the medicines you take.

<u>How should I take AGENERASE Oral Solution?</u>

- Take AGENERASE Oral Solution every day exactly as your healthcare provider has prescribed it**, so it will be as effective as possible**. Your healthcare provider will decide the right dose for you.
- If you miss a dose **by more than 4 hours, wait and take the next dose at the regular time. However, if you miss a dose by fewer than 4 hours, take your missed dose right away. Then take your next dose at the regular time.**
- **Do not take more or less than your prescribed dose of AGENERASE Oral Solution at any one time.** Do not change your dose or stop taking AGENERASE without talking with your healthcare provider.
- You can take AGENERASE Oral Solution with or without food**. However, do not take AGENERASE with a high–fat meal. This could reduce the effectiveness of the medicine.**
- If you take AGENERASE with the **buffered form of VIDEX® (didanosine, ddI), take them at least 1 hour apart.**
- If you take AGENERASE Oral Solution with antacids**, take them at least 1 hour apart.**
- When your supply of AGENERASE or other anti-HIV medicine starts to run low**, arrange to get more from your healthcare provider or pharmacy. The amount of virus in your blood may increase if one or more of the drugs are stopped, even for a short time.**
- Stay under the care of a healthcare provider while using AGENERASE.

What should I avoid while taking AGENERASE?

Do not

- take vitamin E while taking AGENERASE. It contains large amounts of vitamin E.
- take AGENERASE with a high-fat meal. It could reduce the effectiveness of the medicine.

What are the possible side effects of AGENERASE?

AGENERASE can cause a severe or life-threatening rash. Call your healthcare provider right away if you have a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether AGENERASE should be stopped.

Common side effects of AGENERASE are nausea, vomiting, diarrhea, rash, and a tingling

feeling, especially around the mouth, and change in taste. These are usually mild to moderate. Depression and mood problems have also been reported in patients taking AGENERASE.

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.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Other side effects include high blood sugar or diabetes, diabetes complications, high cholesterol, or high triglycerides..

This list of side effects is not complete. Your healthcare provider or pharmacist can give you a more complete list of possible side effects. Talk with your healthcare provider about any concerns about the way you are feeling while you are taking AGENERASE.

How should I store AGENERASE Oral Solution?

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

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use AGENERASE for a condition for which it was not prescribed. Do not give AGENERASE to other people, even if they have the same symptoms you have. It may harm them.

AGENERASE® (amprenavir) Oral Solution

This leaflet summarizes the most important information about AGENERASE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AGENERASE that is written for health professionals.

AGENERASE is a registered trademark of the GlaxoSmithKline group of companies.

*The brands listed are trademarks of their respective owners and are not trademarks of the GlaxoSmithKline group of companies. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its products.

Licensed from

GlaxoSmithKline
Research Triangle Park, NC 27709

Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

Date of Issue

RL-

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
8/2/02 04:43:01 PM
NDA 21-007, NDA 21-039