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## PRODUCT INFORMATION

# AGENERASE<sup>®</sup>

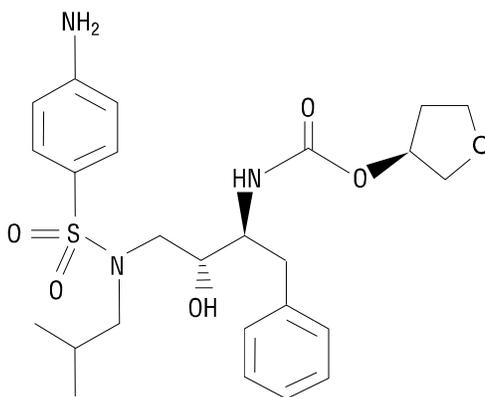
(amprenavir)

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<sub>25</sub>H<sub>35</sub>N<sub>3</sub>O<sub>6</sub>S 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.

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**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<sub>50</sub>) 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.

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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 <sub>0-12</sub> (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

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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:  $6.18 \pm 2.92$  mcg/mL, fasted:  $9.72 \pm 2.75$  mcg/mL),  $T_{\max}$  (fed:  $1.51 \pm 0.68$ , fasted:  $1.05 \pm 0.63$ ), and  $AUC_{0-\infty}$  (fed:  $22.06 \pm 11.6$  mcg•h/mL, fasted:  $28.05 \pm 10.1$  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<sub>1</sub>-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 <sup>14</sup>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 ( $25.76 \pm 14.68$  mcg•h/mL) compared with healthy volunteers ( $12.00 \pm 4.38$  mcg•h/mL). The  $AUC_{0-\infty}$  and  $C_{\max}$  were significantly greater in patients with severe cirrhosis ( $AUC_{0-\infty}$ :  $38.66 \pm 16.08$  mcg•h/mL;  $C_{\max}$ :  $9.43 \pm 2.61$  mcg/mL) compared with healthy volunteers ( $AUC_{0-\infty}$ :  $12.00 \pm 4.38$  mcg•h/mL;  $C_{\max}$ :  $4.90 \pm 1.39$  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

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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.

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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.

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**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 <sub>max</sub>	AUC	C <sub>min</sub>
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 <sup>†</sup> (↓44 to ↓14)	↑64 <sup>†</sup> (↑37 to ↑97)	↑508 <sup>†</sup> (↑394 to ↑649)
Ritonavir	200 mg q.d. for 2 to 4 weeks	1200 mg q.d.	12	↔ <sup>†</sup> (↓17 to ↑30)	↑62 <sup>†</sup> (↑35 to ↑94)	↑319 <sup>†</sup> (↑190 to ↑508)

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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<sub>min</sub> not calculated for single-dose study.

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**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 <sub>max</sub>	AUC	C <sub>min</sub>
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<sub>min</sub> not calculated for single-dose study; ND = Interaction cannot be determined as C<sub>min</sub> was below the lower limit of quantitation.

***Nucleoside Reverse Transcriptase Inhibitors (NRTIs):*** There was no effect of amprenavir on

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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.**

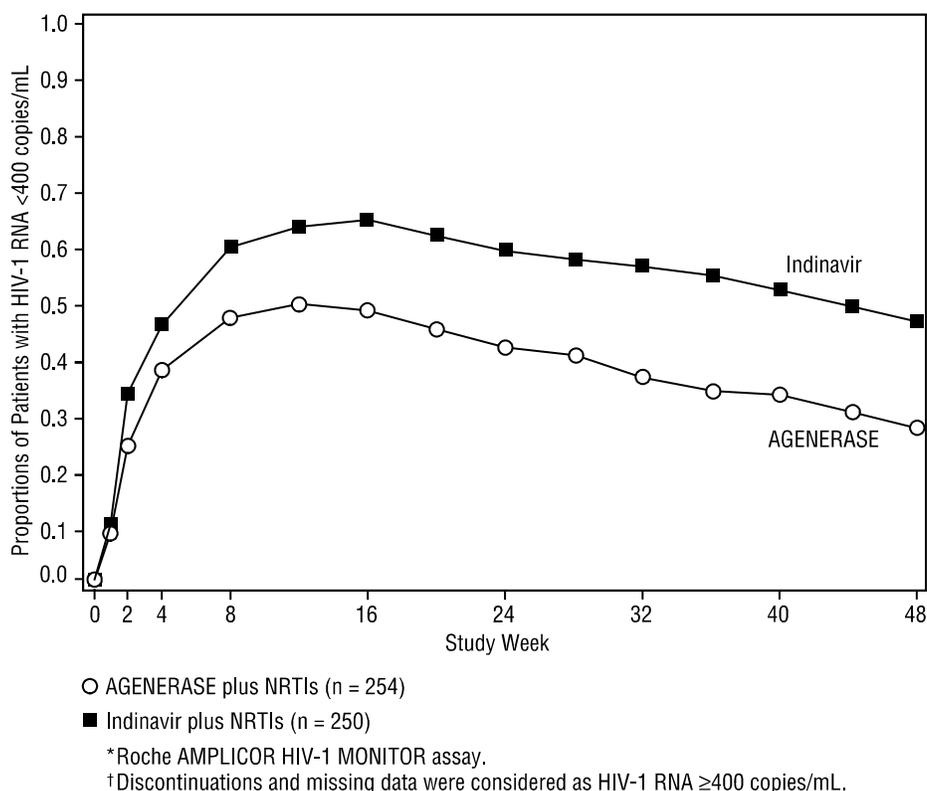
**Description of Clinical Studies: *Therapy-Naive Adults:*** PROAB3001, a randomized, double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) versus lamivudine (150 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

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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<sup>3</sup> (range 9 to 1706 cells/mm<sup>3</sup>) and a median plasma HIV-1 RNA level of 3.93 log<sub>10</sub> copies/mL (range 2.60 to 7.01 log<sub>10</sub> 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<sup>3</sup> versus 144 cells/mm<sup>3</sup>, 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\*†**



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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 <sup>†,‡</sup>	38%	26%
Discontinued due to adverse events <sup>*,‡</sup>	16%	12%
Discontinued due to other reasons <sup>‡,§</sup>	16%	13%

\*Corresponds to rates at Week 48 in Figure 1.

<sup>†</sup>Virological failures at or before Week 48.

<sup>‡</sup>Considered to be treatment failure in the analysis.

<sup>§</sup>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

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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

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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

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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

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**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

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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<sup>®</sup> (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).

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

<b>Drug Class/Drug Name</b>	<b>Clinical Comment</b>
<b>Antimycobacterials:</b> Rifampin	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
<b>Ergot derivatives:</b> Dihydroergotamine, ergonovine, ergotamine, methylergonovine	<b>CONTRAINDICATED</b> 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.
<b>GI motility agents:</b> Cisapride	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Herbal Products:</b> 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.
<b>HMG Co-Reductase Inhibitors:</b> Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
<b>Neuroleptic:</b> Pimozide	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Oral contraceptives:</b> Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to AGENERASE. Alternative methods of non-hormonal contraception are recommended.
<b>Sedative/hypnotics:</b> Midazolam, triazolam	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

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**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
<i>HIV-Antiviral Agents</i>		
<b>Non-nucleoside Reverse Transcriptase Inhibitors:</b> Efavirenz, nevirapine	↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
<b>Non-nucleoside Reverse Transcriptase Inhibitor:</b> Delavirdine	↑Amprenavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
<b>Nucleoside Reverse Transcriptase Inhibitor:</b> Didanosine (buffered formulation only)	↓Amprenavir	Take AGENERASE at least 1 hour before or after the buffered formulation of didanosine.
<b>HIV-Protease Inhibitors:</b> 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.
<b>HIV-Protease Inhibitor:</b> 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	

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<p><b>HIV-Protease Inhibitor:</b> Saquinavir*</p>	<p>Amprenavir's effect on saquinavir is not well established.</p>	<p>Appropriate doses of the combination with respect to safety and efficacy have not been established.</p>
<b><i>Other Agents</i></b>		
<p><b>Antacids</b></p>	<p>↓Amprenavir</p>	<p>Take AGENERASE at least 1 hour before or after antacids.</p>
<p><b>Antiarrhythmics:</b> Amiodarone, lidocaine (systemic), and quinidine</p>	<p>↑Antiarrhythmics</p>	<p>Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with AGENERASE, if available.</p>
<p><b>Antiarrhythmic:</b> Bepridil</p>	<p>↑Bepridil</p>	<p>Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.</p>
<p><b>Anticoagulant:</b> Warfarin</p>		<p>Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.</p>
<p><b>Anticonvulsants:</b> Carbamazepine, phenobarbital, phenytoin</p>	<p>↓Amprenavir</p>	<p>Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.</p>
<p><b>Antifungals:</b> Ketoconazole, itraconazole</p>	<p>↑Ketoconazole ↑Itraconazole</p>	<p>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.</p>
	<p>↑Rifabutin and</p>	<p>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</p>

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<b>Antimycobacterial:</b> Rifabutin*	rifabutin metabolite	neutropenia in patients receiving amprenavir and rifabutin.
<b>Benzodiazepines:</b> Alprazolam, clorazepate, diazepam, flurazepam	↑Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
<b>Calcium Channel Blockers:</b> Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
<b>Corticosteroid:</b> Dexamethasone	↓Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
<b>Erectile Dysfunction Agent:</b> Sildenafil	↑Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
<b>HMG-CoA Reductase Inhibitors:</b> 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.
<b>Immunosuppressants:</b> Cyclosporine, tacrolimus, rapamycin	↑Immunosup- pressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.

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

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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.

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**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.**

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**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)
	<b>Digestive</b>			
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
<b>Skin</b>				
Rash	27%	6%	20%	15%
<b>Nervous</b>				
Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
<b>Psychiatric</b>				
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.

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**Table 10: Selected Laboratory Abnormalities of All Grades  
 Reported in  $\geq 5\%$  of Adult Patients**

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

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

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

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**Concomitant Therapy with Ritonavir:**

**Table 11: Selected Clinical Adverse Events of all Grades Reported in  $\geq 5\%$  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 overdose 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**

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**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).**

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R.P. Scherer  
Beinheim, France  
for

Licensed from



GlaxoSmithKline  
Research Triangle Park, NC 27709



Vertex Pharmaceuticals Incorporated  
Cambridge, MA 02139

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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## PATIENT INFORMATION

### AGENERASE<sup>®</sup> (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.

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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.

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**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<sup>®</sup> (triazolam; used for insomnia)
- CAFERGOT<sup>®</sup> and other ergot medicines (used for migraine headaches)
- PROPULSID<sup>®</sup> (cisapride, used for certain stomach problems)
- VERSED<sup>®</sup> (midazolam; used for sedation)
- ORAP<sup>®</sup> (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<sup>®</sup> (amiodarone; used for certain abnormal heart rhythms)
- Quinidine (used for certain abnormal heart rhythms)
- COUMADIN<sup>®</sup> (warfarin; used for blood thinning)
- Lidocaine (used for certain abnormal heart rhythms)

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- ELAVIL<sup>®</sup> (amitriptyline), TOFRANIL<sup>®</sup> (imipramine) (tricyclic antidepressants)
- SANDIMMUNE<sup>®</sup> or NEORAL<sup>®</sup> (cyclosporine), PROGRAF<sup>®</sup> (tacrolimus), RAPAMUNE<sup>®</sup> (rapamycin or sirolimus) (immunosuppressants)

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

- MYCOBUTIN<sup>®</sup> (rifabutin; used to prevent *Mycobacterium avium* complex [MAC])
- NORVIR<sup>®</sup> (ritonavir; used to treat HIV infection)
- VIAGRA<sup>®</sup> (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<sup>®</sup> (bepridil; used for chronic stable angina)
- RIFADIN<sup>®</sup>, RIFAMATE<sup>®</sup>, RIFATER<sup>®</sup>, or RIMACTANE<sup>®</sup> (rifampin, used for tuberculosis)
- MEVACOR<sup>®</sup> (lovastatin), ZOCOR<sup>®</sup> (simvastatin), and LIPITOR<sup>®</sup> (atorvastatin) (cholesterol-lowering medicines)
- Phenobarbital (used for seizures)
- TEGRETOL<sup>®</sup>, CARBATROL<sup>®</sup> (carbamazepine; used for seizures and trigeminal neuralgia)
- DILANTIN<sup>®</sup> (phenytoin; used for seizures)
- DECADRON<sup>®</sup> (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 all the medicines you**

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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<sup>®</sup> (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**

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**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.

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Date of Issue

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1

## PRODUCT INFORMATION

2 **AGENERASE<sup>®</sup>**

3 **(amprenavir)**

4 **Oral Solution**

5

6 **PATIENT INFORMATION INCLUDED**

7

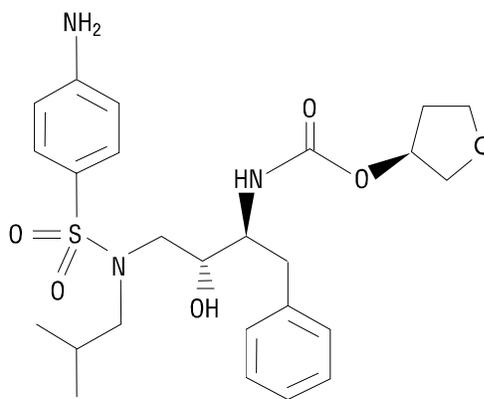
8 Because of the potential risk of toxicity from the large amount of the excipient propylene  
9 glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of  
10 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with  
11 disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

12 AGENERASE Oral Solution should be used only when AGENERASE Capsules or other

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

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<sub>25</sub>H<sub>35</sub>N<sub>3</sub>O<sub>6</sub>S 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.

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

### 37 MICROBIOLOGY:

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

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

50 **Resistance:** HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in*  
51 *vitro* and obtained from patients treated with amprenavir. Genotypic analysis of isolates from  
52 amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid  
53 substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V as well as  
54 mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1 isolates from  
55 21 nucleoside reverse transcriptase inhibitor- (NRTI-) experienced, protease inhibitor-naive  
56 patients treated with amprenavir in combination with NRTIs for 16 to 48 weeks identified  
57 isolates from 15 patients who exhibited a 4- to 17-fold decrease in susceptibility to amprenavir *in*  
58 *vitro* compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir  
59 susceptibility harbored one or more amprenavir-associated mutations. The clinical relevance of  
60 the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation.

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

65

### 66 CLINICAL PHARMACOLOGY:

### AGENERASE<sup>®</sup> (amprenavir) Oral Solution

67 **Pharmacokinetics in Adults:** The pharmacokinetic properties of amprenavir have been studied  
68 in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to  
69 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.

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

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

79

80 **Table 1: Average (%CV) Pharmacokinetic Parameters**  
81 **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%)

82

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

85 **Effects of Food on Oral Absorption:** The relative bioavailability of AGENERASE Capsules  
86 was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal:  
87 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single  
88 1200-mg dose of amprenavir in the fed state compared to the fasted state was associated with  
89 changes in  $C_{max}$  (fed:  $6.18 \pm 2.92$  mcg/mL, fasted:  $9.72 \pm 2.75$  mcg/mL),  $T_{max}$  (fed:  $1.51 \pm 0.68$ ,  
90 fasted:  $1.05 \pm 0.63$ ), and  $AUC_{0-\infty}$  (fed:  $22.06 \pm 11.6$  mcg•h/mL, fasted:  $28.05 \pm 10.1$  mcg•h/mL).

91 AGENERASE may be taken with or without food, but should not be taken with a high-fat meal  
92 (see DOSAGE AND ADMINISTRATION).

### AGENERASE<sup>®</sup> (amprenavir) Oral Solution

93 **Distribution:** The apparent volume of distribution ( $V_z/F$ ) is approximately 430 L in healthy  
94 adult subjects. *In vitro* binding is approximately 90% to plasma proteins. The high affinity  
95 binding protein for amprenavir is alpha<sub>1</sub>-acid glycoprotein (AAG). The partitioning of  
96 amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase,  
97 reflecting the higher amount of unbound drug at higher concentrations.

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

102 AGENERASE Oral Solution contains a large amount of propylene glycol, which is hepatically  
103 metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Alcohol  
104 dehydrogenase (ADH) is present in the human fetal liver at 2 months of gestational age, but at  
105 only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of  
106 postnatal age, ADH activity is equal to or greater than that observed in adults. Additionally,  
107 certain patient groups (females, Asians, Eskimos, Native Americans) may be at increased risk of  
108 propylene glycol-associated adverse events due to diminished ability to metabolize propylene  
109 glycol (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

110 **Elimination:** Excretion of unchanged amprenavir in urine and feces is minimal.  
111 Approximately 14% and 75% of an administered single dose of <sup>14</sup>C-amprenavir can be accounted  
112 for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the  
113 radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to  
114 10.6 hours.

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

117 Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse  
118 events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients  
119 with hepatic impairment. AGENERASE Capsules have been studied in adult patients with  
120 impaired hepatic function using a single 600-mg oral dose. The AUC<sub>0-∞</sub> was significantly greater  
121 in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL) compared with healthy volunteers  
122 (12.00 ± 4.38 mcg•h/mL). The AUC<sub>0-∞</sub> and C<sub>max</sub> were significantly greater in patients with

### AGENERASE<sup>®</sup> (amprenavir) Oral Solution

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

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

128 Patients with renal impairment are at increased risk of propylene glycol-associated adverse  
129 events. Additionally, because metabolites of the excipient propylene glycol in AGENERASE  
130 Oral Solution may alter acid-base balance, patients with renal impairment should be monitored  
131 for potential adverse events (see WARNINGS). AGENERASE Oral Solution should be used  
132 with caution in patients with renal impairment. The impact of renal impairment on amprenavir  
133 elimination has not been studied. The renal elimination of unchanged amprenavir represents <3%  
134 of the administered dose.

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

137 The pharmacokinetics of amprenavir have been studied after either single or repeat doses of  
138 AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected  
139 children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using  
140 25-mg or 150-mg capsules. The  $C_{max}$  of amprenavir increased less than proportionally with dose.  
141 The  $AUC_{0-\infty}$  increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less  
142 bioavailable from the liquid formulation than from the capsules; therefore **AGENERASE**  
143 **Capsules and AGENERASE Oral Solution are not interchangeable on a**  
144 **milligram-per-milligram basis.**

145

**AGENERASE<sup>®</sup> (amprenavir) Oral Solution**

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

Dose	n	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> (hours)	AUC <sub>ss</sub> * (mcg•h/mL)	C <sub>avg</sub> (mcg/mL)	C <sub>min</sub> (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%)

148 \*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C<sub>avg</sub> is a better  
149 comparison of the exposures.

150

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

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

154 Females may have a lower amount of alcohol dehydrogenase compared with males and may be at  
155 increased risk of propylene glycol-associated adverse events; no data are available on propylene  
156 glycol metabolism in females.

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

161 **Drug Interactions:** See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS:  
162 Drug Interactions.

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

168 Drug interaction studies were performed with amprenavir capsules and other drugs likely to be  
169 coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects

**AGENERASE<sup>®</sup> (amprenavir) Oral Solution**

170 of coadministration of amprenavir on the AUC, C<sub>max</sub>, and C<sub>min</sub> are summarized in Table 3 (effect  
171 of other drugs on amprenavir) and Table 4 (effect of amprenavir on other drugs). For information  
172 regarding clinical recommendations, see PRECAUTIONS.

173

**AGENERASE® (amprenavir) Oral Solution**

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 <sub>max</sub>	AUC	C <sub>min</sub>
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 <sup>†</sup> (↓44 to ↓14)	↑64 <sup>†</sup> (↑37 to ↑97)	↑508 <sup>†</sup> (↑394 to ↑649)
Ritonavir	200 mg q.d. for 2 to 4 weeks	1200 mg q.d.	12	↔ <sup>†</sup> (↓17 to ↑30)	↑62 <sup>†</sup> (↑35 to ↑94)	↑319 <sup>†</sup> (↑190 to ↑508)

**AGENERASE<sup>®</sup> (amprenavir) Oral Solution**

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

176 \*Based on total-drug concentrations.

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

178 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ < 10%); NA = C<sub>min</sub> not calculated for single-dose  
 179 study.

180

**AGENERASE® (amprenavir) Oral Solution**

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

181  
182

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
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

183 ↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ < 10%); NA = C<sub>min</sub> not calculated for  
184 single-dose study; ND = Interaction cannot be determined as C<sub>min</sub> was below the lower limit of  
185 quantitation.

186

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

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

189 ***HIV Protease Inhibitors:*** Concurrent use of AGENERASE Oral Solution and NORVIR<sup>®</sup>  
190 (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in  
191 AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same  
192 metabolic pathway for elimination. This combination has not been studied in pediatric patients.

193 The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in  
194 subjects receiving both agents was evaluated using comparisons to historical data. Indinavir  
195 steady-state  $C_{max}$ , AUC, and  $C_{min}$  were decreased by 22%, 38%, and 27%, respectively, by  
196 concomitant amprenavir. Similar decreases in  $C_{max}$  and AUC were seen after the first dose.  
197 Saquinavir steady-state  $C_{max}$ , AUC, and  $C_{min}$  were increased 21%, decreased 19%, and decreased  
198 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state  $C_{max}$ , AUC, and  $C_{min}$  were  
199 increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

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

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

205 For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.  
206

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

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

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

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

216 **There are no data on response to therapy with AGENERASE in protease**

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217 **inhibitor-experienced patients.**

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

220 **Description of Clinical Studies: *Therapy-Naive Adults:*** PROAB3001, a randomized,  
221 double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE  
222 Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg  
223 twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) in  
224 232 patients. Through 24 weeks of therapy, 53% of patients assigned to  
225 AGENERASE/zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Through week 48,  
226 the antiviral response was 41%. Through 24 weeks of therapy, 11% of patients assigned to  
227 zidovudine/lamivudine achieved HIV RNA <400 copies/mL. Antiviral response beyond week 24  
228 is not interpretable because the majority of patients discontinued or changed their antiretroviral  
229 therapy.

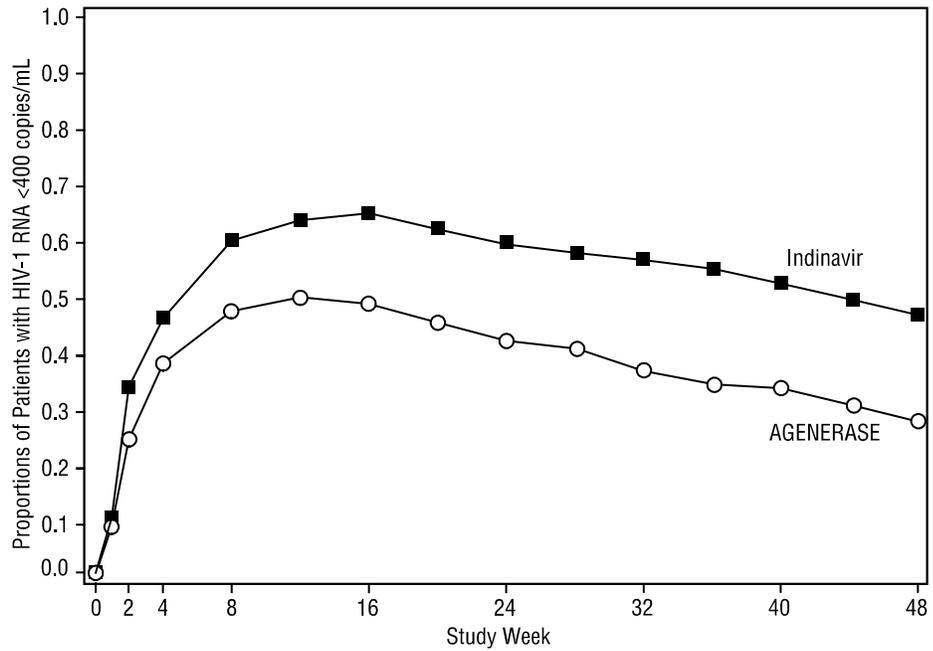
230 ***NRTI-Experienced Adults:*** PROAB3006, a randomized, open-label multicenter study,  
231 compared treatment with AGENERASE Capsules (1200 mg twice daily) plus NRTIs versus  
232 indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease inhibitor-naive  
233 patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80% male, with a median  
234 CD4 cell count of 404 cells/mm<sup>3</sup> (range 9 to 1706 cells/mm<sup>3</sup>) and a median plasma HIV-1 RNA  
235 level of 3.93 log<sub>10</sub> copies/mL (range 2.60 to 7.01 log<sub>10</sub> copies/mL) at baseline. Through 48 weeks  
236 of therapy, the median CD4 cell count increase from baseline in the amprenavir group was  
237 significantly lower than in the indinavir group, 97 cells/mm<sup>3</sup> versus 144 cells/mm<sup>3</sup>, respectively.  
238 There was also a significant difference in the proportions of patients with plasma HIV-1 RNA  
239 levels <400 copies/mL through 48 weeks (see Figure 1 and Table 5).

240

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241

Figure 1: Virologic Response Through Week 48, PROAB3006<sup>\*,†</sup>



○ AGENERASE plus NRTIs (n = 254)

■ Indinavir plus NRTIs (n = 250)

\*Roche AMPLICOR HIV-1 MONITOR assay.

†Discontinuations and missing data were considered as HIV-1 RNA  $\geq$ 400 copies/mL.

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

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247 **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 <sup>†,‡</sup>	38%	26%
Discontinued due to adverse events <sup>*,‡</sup>	16%	12%
Discontinued due to other reasons <sup>‡,§</sup>	16%	13%

248 \*Corresponds to rates at Week 48 in Figure 1.

249 <sup>†</sup>Virological failures at or before Week 48.

250 <sup>‡</sup>Considered to be treatment failure in the analysis.

251 <sup>§</sup>Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations,  
252 non-compliance, pregnancy, never treated, and other reasons.

253

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

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

262

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**Table 6: Drugs That are Contraindicated with AGENERASE Oral Solution**

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

264

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

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

269

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

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

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

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284 **PHARMACOLOGY: Special Populations: Gender and Race).**

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

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

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

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

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

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

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

313 Particular caution should be used when prescribing sildenafil in patients receiving amprenavir.

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314 Coadministration of AGENERASE with sildenafil is expected to substantially increase sildenafil  
315 concentrations and may result in an increase in sildenafil-associated adverse events, including  
316 hypotension, visual changes, and priapism (see PRECAUTIONS: Drug Interactions and  
317 Information for Patients, and the complete prescribing information for sildenafil).

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

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

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

329

#### 330 **PRECAUTIONS:**

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

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

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

343 Formulations of AGENERASE provide high daily doses of vitamin E (see Information for

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

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

353 **Fat Redistribution:** Redistribution/accumulation of body fat, including central obesity,  
354 dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast  
355 enlargement, and “cushingoid appearance,” have been observed in patients receiving  
356 antiretroviral therapy. The mechanism and long-term consequences of these events are currently  
357 unknown. A causal relationship has not been established.

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

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

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

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374 AGENERASE Oral Solution is contraindicated in infants and children below the age of  
375 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with  
376 disulfiram or metronidazole. AGENERASE Oral Solution should be used only when  
377 AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

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

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

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

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

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

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

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

403 Patients should be advised that drinking alcoholic beverages is not recommended while taking

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404 AGENERASE Oral Solution.

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

408 Patients taking AGENERASE should be instructed **not** to use hormonal contraceptives  
409 because some birth control pills (those containing ethinyl estradiol/norethindrone) have been  
410 found to decrease the concentration of amprenavir. Therefore, patients receiving hormonal  
411 contraceptives should be instructed to use alternate contraceptive measures during therapy with  
412 AGENERASE..

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

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

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

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

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

431 AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and therefore  
432 should not be administered concurrently with medications with narrow therapeutic  
433 windows that are substrates of CYP3A4. There are other agents that may result in serious

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434 and/or life-threatening drug interactions (see CONTRAINDICATIONS and  
435 WARNINGS).

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

438

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439

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

<b>Drug Class/Drug Name</b>	<b>Clinical Comment</b>
<b>Alcohol-dependence treatment:</b> Disulfiram	<b>CONTRAINDICATED</b> due to potential risk of toxicity from the large amount of the excipient, propylene glycol, in AGENERASE Oral Solution.
<b>Antibiotic:</b> Metronidazole	<b>CONTRAINDICATED</b> due to potential risk of toxicity from the large amount of the excipient, propylene glycol, in AGENERASE Oral Solution.
<b>Antimycobacterials:</b> Rifampin	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
<b>Ergot derivatives:</b> Dihydroergotamine, ergonovine, ergotamine, methylergonovine	<b>CONTRAINDICATED</b> 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.
<b>GI motility agents:</b> Cisapride	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Herbal Products:</b> 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.
<b>HIV-Protease Inhibitor:</b> 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.
<b>HMG Co-Reductase Inhibitors:</b> Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
<b>Neuroleptic:</b> Pimozide	<b>CONTRAINDICATED</b> due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Oral contraceptives:</b> Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to AGENERASE. Alternative methods of non-hormonal contraception are recommended.

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

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441  
442  
443

**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**

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

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<p><b>HIV-Protease Inhibitor:</b> Ritonavir Capsules*</p>	<p>↑Amprenavir</p>	<p>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.</p>
<p><b>HIV-Protease Inhibitor:</b> Saquinavir*</p>	<p>↓Amprenavir  Amprenavir's effect on saquinavir is not well established.</p>	<p>Appropriate doses of the combination with respect to safety and efficacy have not been established.</p>
<p><i>Other Agents</i></p>		
<p><b>Antacids</b></p>	<p>↓Amprenavir</p>	<p>Take AGENERASE at least 1 hour before or after antacids.</p>
<p><b>Antiarrhythmics:</b> Amiodarone, lidocaine (systemic), and quinidine</p>	<p>↑Antiarrhythmics</p>	<p>Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with AGENERASE, if available.</p>
<p><b>Antiarrhythmic:</b> Bepridil</p>	<p>↑Bepridil</p>	<p>Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.</p>
<p><b>Anticoagulant:</b> Warfarin</p>		<p>Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.</p>
<p><b>Anticonvulsants:</b> Carbamazepine, phenobarbital, phenytoin</p>	<p>↓Amprenavir</p>	<p>Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.</p>
		<p>Increase monitoring for adverse events due to</p>

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<p><b>Antifungals:</b> Ketoconazole, itraconazole</p>	<p>↑Ketoconazole ↑Itraconazole</p>	<p>ketoconazole or itraconazole. Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.</p>
<p><b>Antimycobacterial:</b> Rifabutin*</p>	<p>↑Rifabutin and rifabutin metabolite</p>	<p>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.</p>
<p><b>Benzodiazepines:</b> Alprazolam, clorazepate, diazepam, flurazepam</p>	<p>↑Benzodiazepines</p>	<p>Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.</p>
<p><b>Calcium Channel Blockers:</b> Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine</p>	<p>↑Calcium channel blockers</p>	<p>Caution is warranted and clinical monitoring of patients is recommended.</p>
<p><b>Corticosteroid:</b> Dexamethasone</p>	<p>↓Amprenavir</p>	<p>Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.</p>
<p><b>Erectile Dysfunction Agent:</b> Sildenafil</p>	<p>↑Sildenafil</p>	<p>Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.</p>
<p><b>HMG-CoA Reductase Inhibitors:</b> Atorvastatin</p>	<p>↑Atorvastatin</p>	<p>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.</p>

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<b>Immunosuppressants:</b> Cyclosporine, tacrolimus, rapamycin	↑Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.
<b>Narcotic analgesics:</b> Methadone*	↓Amprenavir  ↓Methadone	AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered.  Dosage of methadone may need to be increased when coadministered with AGENERASE.
<b>Tricyclic Antidepressants:</b> Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with AGENERASE.

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

445

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

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

457 **Pregnancy and Reproduction:** AGENERASE Oral Solution is contraindicated during  
458 pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol  
459 content. Therefore, if AGENERASE is used in pregnant women, the AGENERASE

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460 Capsules formulation should be used (see complete prescribing information for  
461 AGENERASE Capsules).

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

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

471 **Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children**  
472 **below the age of 4 years due to the potential risk of toxicity from the excipient propylene**  
473 **glycol (see CONTRAINDICATIONS and WARNINGS).** Alcohol dehydrogenase (ADH),  
474 which metabolizes propylene glycol, is present in the human fetal liver at 2 months of gestational  
475 age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to  
476 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

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

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

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

488

489 **ADVERSE REACTIONS:** In clinical studies, adverse events leading to amprenavir

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490 discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due to  
491 gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort), which were  
492 mild to moderate in severity.

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

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

504

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505 **Table 9: Selected Clinical Adverse Events of All Grades Reported in >5% of Adult**  
506 **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)
	<b>Digestive</b>			
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
<b>Skin</b>				
Rash	27%	6%	20%	15%
<b>Nervous</b>				
Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
<b>Psychiatric</b>				
Depressive or mood disorders	16%	4%	9%	13%

507 \*AGENERASE Capsules.

508

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

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512

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

514

**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%
Hypertriglyceridemia (>213 mg/dL)	41%	27%	56%	52%
Hypercholesterolemia (>283 mg/dL)	7%	3%	13%	15%

515 \*AGENERASE Capsules.

516

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

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

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521 **Concomitant Therapy with Ritonavir:**

522 **Table 11: Selected Clinical Adverse Events of all Grades Reported in ≥5% of Adult**  
523 **Patients in Ongoing, Open-Label Clinical Trials of AGENERASE Capsules in**  
524 **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%

525 \*Data from 2 ongoing, open-label studies in treatment-naïve patients also receiving  
526 abacavir/lamivudine.

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

529

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

533

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

538 AGENERASE Oral Solution contains large amounts of propylene glycol. In the event of  
539 overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene

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540 glycol can be removed by hemodialysis.

541

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

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

552

553 **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

554

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

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

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

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563 with hepatic impairment. Based on a study with AGENERASE Capsules, adult patients with a  
564 Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Oral  
565 Solution of 513 mg (34 mL) twice daily, and adult patients with a Child-Pugh score ranging from  
566 9 to 12 should receive a reduced dose of AGENERASE Oral Solution of 342 mg (23 mL) twice  
567 daily (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency).

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

569 **Renal Insufficiency:** AGENERASE Oral Solution is contraindicated in patients with renal  
570 failure (see CONTRAINDICATIONS).

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

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

576

#### 577 **HOW SUPPLIED:**

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

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

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

583

584

585

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588 Research Triangle Park, NC 27709

589



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Cambridge, MA 02139

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591

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594

595 Date of Issue RL-

596

597 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

598 -----

599

600 **PATIENT INFORMATION**

601

602 **AGENERASE<sup>®</sup> (amprenavir) Oral Solution**

603

604 **ALERT: Find out about medicines that should not be taken with AGENERASE**  
605 **Oral Solution. Read the section: “What important information should I know about**  
606 **taking AGENERASE Oral Solution with other medicines?”**

607

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

612

613 **What is the most important information I should know about AGENERASE?**  
614 **AGENERASE can cause serious and life-threatening side effects if you take it with**  
615 **certain other medicines. For information about these medicines, see the section**  
616 **“What important information should I know about taking AGENERASE with**  
617 **other medicines?”**

618

619 **What is AGENERASE Oral Solution?**

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

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

622 class of anti-HIV medicines called protease inhibitors.

623

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

628

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

633

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

636

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

640

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

643

### 644 **Who should not take AGENERASE Oral Solution?**

645 AGENERASE Oral Solution contains a large amount of propylene glycol, a liquid needed to  
646 dissolve amprenavir. Because of the possible side effects of the large amount of propylene glycol,  
647 AGENERASE Oral Solution should be used only when AGENERASE Capsules or other  
648 protease inhibitor formulations are not options.

649

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

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

652 AGENERASE Oral Solution.

653

654 **Do not take AGENERASE Oral Solution if**

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

659

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

662

663 **Tell your healthcare provider if**

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

667

668 **Tell your healthcare provider about all your medical conditions.** AGENERASE Oral

669 Solution may not be right for you, or you may need a dosage change in AGENERASE. Be sure to  
670 tell your healthcare provider if you

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

674

675 **What important information should I know about taking AGENERASE Oral**

676 **Solution with other medicines?**

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

681

### AGENERASE<sup>®</sup> (amprenavir) Oral Solution

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

684

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

688

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

690

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

- 693 ▪ FLAGYL<sup>®</sup> (metronidazole, used to treat certain infections)
- 694 ▪ ANTABUSE<sup>®</sup> (disulfiram, used to treat alcohol dependence)
- 695 ▪ HALCION<sup>®</sup> (triazolam; used for insomnia)
- 696 ▪ CAFERGOT<sup>®</sup> and other ergot medicines (used for migraine headaches)
- 697 ▪ PROPULSID<sup>®</sup> (cisapride, used for certain stomach problems)
- 698 ▪ VERSED<sup>®</sup> (midazolam; used for sedation)
- 699 ▪ ORAP<sup>®</sup> (pimozide; used for Tourette's disorder)

700

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

- 703 ▪ CORDARONE<sup>®</sup> (amiodarone; used for certain abnormal heart rhythms)
- 704 ▪ Quinidine (used for certain abnormal heart rhythms)
- 705 ▪ COUMADIN<sup>®</sup> (warfarin; used for blood thinning)
- 706 ▪ Lidocaine (used for certain abnormal heart rhythms)
- 707 ▪ ELAVIL<sup>®</sup> (amitriptyline), TOFRANIL<sup>®</sup> (imipramine) (tricyclic antidepressants)
- 708 ▪ SANDIMMUNE<sup>®</sup> or NEORAL<sup>®</sup> (cyclosporine), PROGRAF<sup>®</sup> (tacrolimus), RAPAMUNE<sup>®</sup>  
709 (rapamycin or sirolimus) (immunosuppressants)

710

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

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

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

718

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

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

736

737 **This list is not complete. Be sure to tell your healthcare provider about all the medicines**  
738 **you take.**

739

740 **How should I take AGENERASE Oral Solution?**

## AGENERASE<sup>®</sup> (amprenavir) Oral Solution

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

759

### What should I avoid while taking AGENERASE?

#### **Do not**

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

764

### What are the possible side effects of AGENERASE?

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

769

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

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771 feeling, especially around the mouth, and change in taste. These are usually mild to moderate.

772 Depression and mood problems have also been reported in patients taking AGENERASE.

773

774 **Possible side effects from the large amount of propylene glycol** in AGENERASE Oral

775 Solution include seizures, drowsiness, fast heart rate, and kidney and blood abnormalities.

776

777 Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes

778 may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and

779 around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and

780 long-term health effects of these conditions are not known at this time.

781

782 **Other side effects** include high blood sugar or diabetes, diabetes complications, high cholesterol,

783 or high triglycerides..

784

785 **This list of side effects is not complete.** Your healthcare provider or pharmacist can give you a

786 more complete list of possible side effects. Talk with your healthcare provider about any

787 concerns about the way you are feeling while you are taking AGENERASE.

788

789 **How should I store AGENERASE Oral Solution?**

790 AGENERASE Oral Solution should be stored at room temperature and should not be

791 refrigerated.

792

793 **General advice about prescription medicines**

794 Medicines are sometimes prescribed for conditions that are not mentioned in patient information

795 leaflets. Do not use AGENERASE for a condition for which it was not prescribed. Do not give

796 AGENERASE to other people, even if they have the same symptoms you have. It may harm

797 them.

798

**AGENERASE<sup>®</sup> (amprenavir) Oral Solution**

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

802

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804

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806 GlaxoSmithKline group of companies. The makers of these brands are not affiliated with and do  
807 not endorse GlaxoSmithKline or its products.

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/s/

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