AGENERASE™

(amprenavir)

Capsules

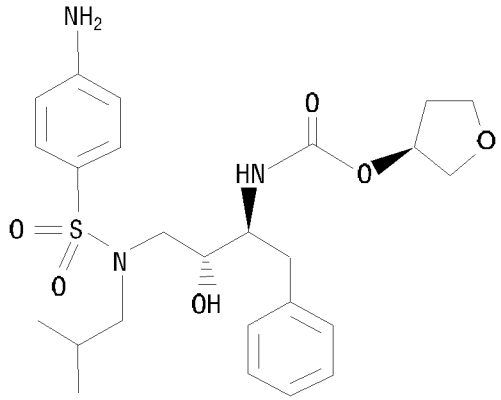
AGENERASE™

(amprenavir)

Oral Solution

AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE.

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



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

AGENERASE Capsules are available for oral administration in strengths of 50 and 150 mg. Each capsule contains the inactive ingredients d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400), and propylene glycol. 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 d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS). The total amount of vitamin E in the recommended daily adult dose of AGENERASE is 1744 IU.

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), TPGS, menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400), propylene glycol, 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 d-alpha tocopheryl polyethylene glycol 1000 succinate.

MICROBIOLOGY:

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

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

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro* and were also 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 M46I/L, I47V, I50V, I54L/V, and I84V as well as mutations in the viral protease p1/p6 cleavage site. Phenotypic analysis of HIV-1 isolates from some patients on amprenavir monotherapy for 8 to 12 weeks showed a 5- to 10-fold decrease in susceptibility to amprenavir *in vitro* compared to baseline. Phenotypic analysis of HIV-1 isolates from 28 patients treated with amprenavir in combination with zidovudine and lamivudine for 16 to 36 weeks identified isolates from six patients that exhibited a 5- to 11-fold decrease in susceptibility to amprenavir *in vitro* compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy has not been established.

Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. The potential for protease inhibitor cross–resistance in HIV-1 isolates from amprenavir-treated patients has not been fully evaluated.

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 (n = 5)

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)
5.36 (62%)	1.9 (51%)	18.5 (63%)	1.54 (63%)	0.28 (52%)	31 (132%)

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

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

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

increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

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

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

Special Populations: ***Hepatic Insufficiency:*** AGENERASE has been studied in adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•h/mL). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•h/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$: 12.00 ± 4.38 mcg•h/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

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

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

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

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

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

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

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

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

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

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

Drug interaction studies were performed with amprenavir 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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