

Selected Properties of Amprenavir

****sale and distribution of capsules discontinued in December 2006; amprenavir oral solution still available**

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| Other names | Agenerase®, 141W94 |
| Manufacturer | GlaxoSmithKline |
| Pharmacology/Mechanism of Action | HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions. |
| Activity | IC ₉₀ : 0.08 uM (in vitro) Highly specific for HIV-1 and HIV-2 <i>in vitro</i> – synergistic with ZDV, ABC, ddI, SQV; additive activity with IDV and RTV |
| Resistance - genotypic | Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: I50V, I84V Minor: L10F/I/R/V, V32I, M46I/L, I47V, I54L/V/M, G73S, V82A/F/S/T, L90M <i>*as major & minor mutations accumulate, susceptibility to PIs decreases</i> |
| Resistance - phenotypic | Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): I50V: 8-fold ↑ (intermediate-to-high-level resistance) I84V: 3.9-fold ↑ (clinical resistance) |
| Cross-Resistance | <i>In vitro</i> , amprenavir-resistant isolates are highly susceptible to indinavir, saquinavir, and nelfinavir, but show reduced susceptibility to ritonavir. The principal protease mutation associated with cross-resistance to amprenavir following treatment failure with other protease inhibitors was I84V, particularly when mutations L10I/V/F were also present. |
| Oral Bioavailability | F=25-29% in rats NB: Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore AGENERASE Capsules and AGENERASE Oral Solution are <u>not</u> interchangeable on a milligram per milligram basis." |

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| Effect of Food | Food ↓ AUC by 23%, however no food restrictions recommended. High fat meal should be avoided. Avoid consuming alcoholic beverages while taking amprenavir oral solution. |
| Protein Binding | ~90% plasma protein bound (mainly AAG) |
| Vd | ~430L in healthy adults |
| Tmax | 1-2 hours |
| serum T_{1/2} | 7.1-10.6 hours |
| Drug Concentrations | 1200 mg BID dosing: C _{max,ss} 7.06 µg/ml; C _{min,ss} 0.63 µg/ml 600 mg/100 mg ritonavir BID (Goujard et al. 2003): C _{min,ss} 1.92 ug/mL, C _{max,ss} 7.12 ug/mL, AUC _{ss} 35.74 ug.h/mL. In vivo intracellular accumulation: cell/plasma ratio 0.36 (amprenavir alone), 3.2 (range 1.1-11.4) when dosed with ritonavir. |
| Minimum target trough concentrations (for wildtype virus) | 0.4 mg/mL |
| CSF (% of serum) | CSF/Plasma ratio: 0.45 – 1.30% (3 patients) |
| Metabolism | Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir). |
| Excretion | Primarily hepatic metabolized. Excretion via biliary route. |

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| <p>Dosing – Adult</p> | <p>Capsules: 1200 mg po BID</p> <ul style="list-style-type: none"> - <i>1200 mg once daily with ritonavir 200 mg once daily</i> - <i>600 mg po BID with ritonavir 100 mg BID</i> - Capsule contains significant amount of vitamin E (109 IU vitamin E as d-alpha TGPS per 150-mg amprenavir capsule), to yield a total Vitamin E dose of 1744 IU associated with the recommended adult daily dose. Therefore, avoid additional vitamin E supplements. <p>Solution: 1400 mg po BID</p> <p>Administer liquid solution of amprenavir at least 1 hour apart from other medications that contain sorbitol.</p> <ul style="list-style-type: none"> - Each 1 mL oral amprenavir solution contains 46 IU vitamin E as d-alpha TPGS (tocopheryl polyethylene glycol 1000 succinate). Thus, do not administer an equivalent adult dose in liquid form since the total daily dose of Vitamin E would approach 7400 IU, which is several hundred times the adult Vitamin E reference daily intake of 30 IU. |
| <p>Dosing – Pediatric</p> | <p>Pediatric (< 50kg and > 4 yrs): Solution: 22.5 mg/kg/dose po bid or 17 mg/kg/dose po tid Capsules: 20 mg/kg/dose po bid or 15 mg/kg/dose po tid</p> <p>Note:</p> <ul style="list-style-type: none"> - do not use in neonates, children < 4yrs, pregnant woman (vitamin E & propylene glycol toxicity) - capsules and solution are different doses |
| <p>Special instructions for pediatric patients</p> | <ul style="list-style-type: none"> • liquid in capsule is unpalatable • do not use in children < 4 yrs (vitamin E and propylene glycol toxicity), pregnant women, patients with hepatic or renal failure and patients treated with disulfiram or metronidazole • do not take vitamin E supplement (46 IU/ml) (daily recommendation for children 10 IU/day) • do not use in neonates¹ (propylene glycol t_{1/2} neonate = 16.9 hours, t_{1/2} adult = 5 hours) • avoid co-administration of amprenavir solution with ritonavir solution. Amprenavir solution contains propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. A competitive metabolic interaction with propylene glycol contained in amprenavir (550 mg/ml) & ethanol in ritonavir (43% v/v ethanol) may occur. Both are substrates of alcohol dehydrogenase. |

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| <p>Adjust in Liver Dysfunction</p> | <p>The AUC was significantly greater in patients with moderate cirrhosis ($25.76 \pm 14.68 \text{mcg}\cdot\text{h/mL}$) compared with healthy volunteers ($12.00 \pm 4.38 \text{mcg}\cdot\text{h/mL}$). The AUC and C_{max} were significantly greater in patients with severe cirrhosis (AUC: $38.66 \pm 16.08 \text{mcg}\cdot\text{h/mL}$; C_{max}: $9.43 \pm 2.61 \text{mcg/mL}$) compared with healthy volunteers (AUC: $12.00 \pm 4.38 \text{mcg}\cdot\text{h/mL}$; C_{max}: $4.90 \pm 1.39 \text{mcg/mL}$). Patients with impaired hepatic function require dosage adjustment.</p> <p>In order to obtain AUC equivalent to 1200 mg BID in patients without cirrhosis, the following dosage reductions are suggested [Veronese et al, 2000]:</p> <p>Child-Pugh score 5-8: 450 mg BID</p> <p>Child-Pugh score 9-12: 300 mg BID</p> |
| <p>Adjust in Renal Failure/Dialysis</p> | <p>Dosage adjustment not required</p> |
| <p>Toxicity</p> | <p>Side effects occurring in >10% of patients: rash (20-27%), SJS (1%), diarrhea, nausea, vomiting, headache; other: paresthesia, perioral tingling/numbness, hemolytic anemia (rare).</p> <p>Other: Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.</p> <p>Warning: As amprenavir is a sulfonamide, there is potential for cross sensitivity in people with sulfonamide allergies.</p> <p>Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, amprenavir oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole.</p> |
| <p>Pregnancy & Lactation</p> | <p>Pregnancy risk category C. Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, amprenavir oral solution is contraindicated in pregnant women.</p> |
| <p>Drug Interactions</p> | <p>Amprenavir is an inhibitor of CYP3A4. The concomitant administration of amprenavir oral solution with disulfiram or other medicinal products that reduce alcohol metabolism (e.g. or preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol is contraindicated.</p> <p>See separate Drug Interaction Table.</p> |

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| Baseline Assessment | Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile. |
| Routine Labs | CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months. |
| Dosage Forms | Liquid: 15 mg/ml oral solution, 240 mL bottle, DIN 02243543 **sale and distribution of capsules discontinued in December 2006 Capsules (off-white to cream colored soft gelatin capsules): - 50 mg capsules, DIN 02243541 (480/bottle) - 150 mg capsules, DIN 02243542 (240/bottle) |
| Storage | Both caps and liquid- store at room temperature in tightly sealed container. |

References:

Ford J, Khoo SH, Back DJ. The intracellular pharmacology of antiretroviral protease inhibitors. JAC 2004 (advance on-line publication).

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Veronese L, Rautaureau J, Sadler BM, Gillotin C, Petite J-P, Pillegand B, et al. Single-dose pharmacokinetics of amprenavir, a human immunodeficiency virus type 1 protease inhibitor, in subjects with normal or impaired hepatic function. Antimicrob Agents Chemother 2000;44:821-6.