

## **Amprenavir (Agenerase®)**

### **Class:**

HIV protease inhibitor.

### **Antiviral Activity:**

Amprenavir inhibits both HIV-1 and HIV-2 *in vitro*; however, it has FDA approval on it for HIV-1.

### **Mechanism of Action:**

Amprenavir forms an inhibitor-enzyme complex with HIV protease preventing the normal maturation process of HIV and the formation to mature infectious virions.

### **Mechanism of Resistance:**

Higher levels of protease inhibitor resistance result from the accumulation of multiple protease inhibitor-resistance mutations. The many mechanisms of resistance include reduced binding affinity between the inhibitor and the protease enzyme, alterations in enzyme catalysis, effects on dimer stability, alterations in inhibitor binding kinetics, and re-shaping of the active site.

### **Pharmacodynamics:**

The concentration of amprenavir required to inhibit 50% (IC50) of wild-type HIV isolates is  $14.6 \pm 12.5$ ng/mL.

### **Pharmacokinetics:**

Amprenavir is 90% bound to plasma proteins with high affinity binding to alpha1-acid glycoprotein. The majority of metabolism of amprenavir occurs in the liver by the cytochrome P450 (CYP) enzyme 3A4A. Amprenavir oral solution is 14% less bioavailable than the capsule formulation. Seventy five percent of a single dose of amprenavir is excreted in the feces and 14% in the urine.

### **Adverse Effects:**

Common adverse effects are nausea, diarrhea, rash, vomiting, headache, and gaseous symptoms. Hypertriglyceridemia, AST and ALT elevations, and hyperbilirubinemia have also been seen.

### **Dosage:**

Capsule 50mg

Oral Solution 15mg/ml

Amprenavir capsules and oral solution are not interchangeable on a milligram-per-milligram basis.

#### **Capsule:**

Adult – 1200mg twice daily OR amprenavir 600mg and ritonavir 100mg twice daily OR Amprenavir 1200mg and ritonavir 200mg once daily

Pediatric (4 to 16 years old and <50kg) – 20mg/kg twice daily or 15mg/kg 3 times a day

(max 2400mg daily)

**Solution:**

13-16 years and = 50kg or >16 years old – 1400mg twice daily

13-16 and <50kg or children age 4-12 years – 22.5 mg/kg (1.5ml/kg) twice daily OR 17 mg/kg (1.1mL/kg) three times daily (max dose of 2800 mg daily).

The oral solution contains a large amount of propylene glycol and should only be used if a patient cannot tolerate the capsule formulation. The oral solution should not be given to patients with renal or hepatic insufficiency or patients who are pregnant.

**Disease state based dosing:**

Renal Impairment: no dose adjustment

Hepatic Impairment:

Use with caution in patients with moderate or severe hepatic impairment

Child-Pugh score of 5 to 8 – 450 mg twice daily (capsule formulation)

Child-Pugh score of 9 to 12 – 300mg twice daily (capsule formulation)

**Contraindications/Warnings/ Precautions:**

Amprenavir is contraindicated with:

dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam and triazolam

Amprenavir oral solution contains a large amount of propylene glycol and may lead to toxicity.

**Drug Interactions:**

Amprenavir is metabolized by, inhibits and induces the CYP450 3A4 enzyme. Therefore medications that are also metabolized by CYP450 3A4 may interact with amprenavir.

**Pregnancy:**

Category C: Risk unknown. Human studies inadequate.

**Monitoring Requirements:**

Blood glucose, lipid profile

**Brand names/Manufacturer:**

Agenerase®, Lexiva (fosamprenavir), GlaxoSmithkline