

### Selected Properties of Fosamprenavir

<b>Other names</b>	Telzir®, Lexiva® (US), GW433-908
<b>Manufacturer</b>	ViiV Healthcare Shire Canada
<b>Pharmacology/Mechanism of Action</b>	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.
<b>Activity</b>	IC <sub>90</sub> : 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
<b>Resistance - genotypic</b>	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 &amp; minor mutations accumulate, susceptibility to PIs decreases</i>
<b>Resistance - phenotypic</b>	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ ( <a href="http://hivdb.stanford.edu/">http://hivdb.stanford.edu/</a> ): I50V: 8-fold ↑ (intermediate-to-high-level resistance) I84V: 3.9-fold ↑ (clinical resistance)
<b>Cross-Resistance</b>	<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.
<b>Oral Bioavailability</b>	Fosamprenavir is a prodrug that is rapidly hydrolyzed to amprenavir via enzymes in the gut epithelium. The absolute bioavailability of amprenavir has not been determined in humans.
<b>Effect of Food</b>	<b>Tablets:</b> May be taken with or without food. A high fat meal (967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) had no significant effect on standard amprenavir kinetic parameters.  <b>Oral suspension: Take on an empty stomach.</b> Administration of the fosamprenavir calcium oral suspension formulation with a high fat meal reduced plasma amprenavir AUC by approximately 25% and C <sub>max</sub> by approximately 40% as compared to the fasted state.  NB: U.S. product monograph states that adults should take the oral suspension without food; pediatric patients should take the suspension <u>with</u> food.
<b>Protein Binding</b>	~90% plasma protein bound (mainly AAG)

<b>Vd</b>	~430L in healthy adults or approximately 6 L/kg, with penetration freely into tissues beyond the systemic circulation (amprenavir). This value decreases approximately 40% when fosamprenavir is coadministered with ritonavir, most likely due to an increase in amprenavir bioavailability.
<b>Tmax</b>	1.5-4 hours (median 2.5 hours)
<b>serum T ½</b>	7.7 hours
<b>Drug Concentrations</b>	<p>Median steady-state plasma amprenavir pharmacokinetic values:</p> <ul style="list-style-type: none"> <li>• 1400 mg BID dosing : Cmax 4.82 ug/mL, Cmin 0.35 ug/mL, AUC<sub>24</sub> 33 ug.h/mL</li> <li>• 1400 mg QD/ritonavir 200 mg QD dosing: Cmax 7.24 ug/mL, Cmin 1.45 ug/mL, AUC<sub>24</sub> 69.4 ug.h/mL</li> <li>• 700 mg BID/ritonavir 100 mg BID dosing: Cmax 6.08 ug/mL, Cmin 2.12 ug/mL, AUC<sub>24</sub> 79.2 ug.h/mL</li> </ul> <p>In a retrospective analysis of 15 HIV/HCV coinfecting patients without cirrhosis receiving fosamprenavir 1400 mg BID, mean amprenavir AUC<sub>12</sub> was 35.3 mg.h/L, mean Ctrough 1.2 mg/L.[Barbarini G et al. 2009]</p>
<b>Minimum target trough concentrations (for wildtype virus)</b>	0.4 mg/mL (unboosted amprenavir)
<b>CSF (% of serum)</b>	<p>CSF/Plasma ratio: 0.45 – 1.30% (3 patients) (amprenavir)</p> <p>In 43 HIV-infected subjects on fosamprenavir regimens with matched CSF &amp; plasma samples, amprenavir was present in all CSF samples, median 24 ng/mL. The median amprenavir CSF:plasma ratio was 0.013. CSF concentrations were not significantly different between those taking FPV/r vs. FPV (41 vs. 12 ng/mL, p=0.10). Amprenavir CSF concentrations &gt;IC<sub>50</sub>wt (5.6 ng/mL) in 42/43 samples by median 4.3 fold (IQR 2.9-7.8). Therefore, amprenavir is present in CSF at sufficiently high levels to inhibit wild-type HIV.[Letendre et al. 2009]</p> <p>2010 CNS Penetration Effectiveness (CPE) Score: 3 (boosted fosamprenavir), 2 (unboosted fosamprenavir) [Letendre S et al. 2010]</p>
<b>Metabolism</b>	Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir). Data also suggest that amprenavir induces CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).
<b>Excretion</b>	Primarily hepatic metabolized. Excretion via biliary route.
<b>Dosing – Adult</b>	<p>PI-Naïve subjects:</p> <ul style="list-style-type: none"> <li>• <b>700 mg/100 mg ritonavir po BID</b></li> <li>• <b>1400 mg/200 mg ritonavir po QD</b></li> <li>• <b>1400 mg/100 mg ritonavir po QD (US monograph)</b></li> <li>• <b>1400 mg BID (U.S. monograph only)</b></li> </ul> <p>PI-Experienced subjects:</p>

	<ul style="list-style-type: none"> <li>• <b>700 mg/100 mg ritonavir po BID</b></li> </ul>
<b>Dosing – Pediatric</b>	<p><i>Canadian monograph information:</i>  <b>Children (&lt; 12 years of age) and Adolescents (12 to 18 years of age):</b>  The safety and efficacy of TELZIR® in combination with ritonavir have not yet been established in these patient populations.</p> <p><i>American monograph information:</i>  <b>Pediatric Patients (2 to 18 years of age)</b>  The recommended dosage of LEXIVA in patients ≥2 years of age should be calculated based on body weight (kg) and should not exceed the recommended adult dose. The data are insufficient to recommend: (1) once-daily dosing of LEXIVA alone or in combination with ritonavir, and (2) any dosing of LEXIVA in therapy-experienced patients 2 to 5 years of age.</p> <p><u>Therapy-Naive 2 to 5 Years of Age:</u>  LEXIVA Oral Suspension 30 mg/g twice daily, not to exceed the adult dose of LEXIVA 1,400 mg twice daily.</p> <p><u>Therapy-Naive &gt;6 Years of Age:</u>  Either LEXIVA Oral Suspension 30 mg/kg twice daily not to exceed the adult dose of LEXIVA 1,400 mg twice daily or LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice daily.</p> <p><u>Therapy-Experienced ≥6 Years of Age:</u>  LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg administered twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice daily.</p> <p>When administered without ritonavir, the adult regimen of LEXIVA Tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg.  When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.</p>
<b>Special instructions for pediatric patients</b>	U.S. product monograph states that pediatric patients should take the suspension <u>with</u> food.
<b>Adjust in Liver Dysfunction</b>	<p>The following dose reductions are recommended:</p> <p><u>Mild Hepatic Impairment</u> (Child-Pugh score ranging from 5 to 6): fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced).</p> <p><u>Moderate Hepatic Impairment</u> (Child-Pugh score ranging from 7 to 9): fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily (therapy-naive) without ritonavir, or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced).</p> <p><u>Severe Hepatic Impairment</u> (Child-Pugh score ranging from 10 to 12): fosamprenavir should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naive).</p>

	<p>The impact of mild, moderate and severe hepatic impairment on the pharmacokinetics of fosamprenavir/ritonavir in HIV-infected subjects was investigated. Subjects with normal hepatic function received fosamprenavir 700 mg/ritonavir 100 mg BID, while subjects with hepatic impairment received modified doses. In subjects with <b>mild hepatic impairment</b>, fosamprenavir 700 mg BID plus ritonavir 100 mg QD resulted in 17% ↑ C<sub>max</sub>, 22% ↑ AUC, similar C<sub>tau</sub> of amprenavir compared to subjects with normal hepatic function. In subjects with <b>moderate hepatic impairment</b>, fosamprenavir 300 mg BID plus ritonavir 100 mg QD yielded 27% ↓ C<sub>max</sub> and AUC, 57% ↓ C<sub>tau</sub> of amprenavir. In subjects with <b>severe hepatic impairment</b>, fosamprenavir 300 mg BID plus ritonavir 100 mg QD yielded 19% ↓ C<sub>max</sub>, 23% ↓ AUC, 38% ↓ C<sub>tau</sub> of amprenavir. No significant safety issues were identified, but plasma amprenavir and ritonavir concentrations were more variable in subjects with impaired hepatic function.[Pérez-Elías et al. 2009]</p>
<b>Adjust in Renal Failure/Dialysis</b>	Dosage adjustment not required.
<b>Toxicity</b>	<p>rash 19% (SJS &lt; 1%), diarrhea, nausea, vomiting, headache, perioral tingling/numbness, hemolytic anemia (rare).  <b>Other:</b> Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.  <b>Warning:</b> As amprenavir is a sulfonamide, there is potential for cross sensitivity in people with sulfonamide allergies.</p>
<b>Pregnancy &amp; Lactation</b>	<p>Pregnancy risk category C. Not recommended due to lack of human data in pregnancy.</p> <p>In 2 HIV-infected pregnant women receiving fosamprenavir (all VL&lt;40 copies/mL at delivery), mean fosamprenavir cord:mother blood concentration ratio was 0.21 (SD +/- 0.01); cord blood concentrations were below cut-off values in both samples. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].</p>
<b>Drug Interactions</b>	Amprenavir is an inhibitor of CYP3A4. See separate Drug Interaction Table.
<b>Baseline Assessment</b>	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.
<b>Routine Labs</b>	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.
<b>Dosage Forms</b>	700 mg pink film-coated tablets, DIN 02261545; 50 mg/mL grape bubblegum and peppermint flavoured oral suspension, 225 mL bottle, DIN 02261553.
<b>Storage</b>	Bottles of 60 tablets. Store at room temperature in tightly sealed container.

	Store oral suspension between 2-30°C. Do not freeze. <b>Discard the suspension 28 days after first opening.</b>
--	---

**References:**

Barbarini G, Villani P, Cusato M, Sangiovanni L, Carbonara S, Ciraci E, et al. Free and total plasma concentrations of amprenavir in HIV-positive patients with hepatitis co-infection treated with unboosted fosamprenavir [abstract P\_38]. 10<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 15-17, 2009.

FDA approves administration of LEXIVA® with lower dose of "boosting" medication ritonavir [press release]. Research Triangle Park, NC: GlaxoSmithKline, Inc; October 12, 2007. (<http://us.gsk.com/ControllerServlet?appld=4&pageld=402&newsid=1158>)

GlaxoSmithKline Inc. Telzir Product monograph. Mississauga, ON, Canada, May 27, 2009.

Ivanovic J, Nicastrì E, Viscione M, Bellagamba R, Signore F, Pisani G et al. Cord blood and amniotic fluid exposures of protease inhibitors and viral load quantification in HIV-infected pregnant women [abstract WEPE0100]. XVIII International AIDS Conference, Vienna, Austria, July 18-23<sup>rd</sup>, 2010.

Letendre S, Best B, Rossi S, Way L, Grant I, Ellis R, et al. Therapeutic amprenavir and abacavir concentrations in CSF from the same individuals [abstract P\_18]. 10<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 15-17, 2009.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Mallolas J et al. Fosamprenavir/ritonavir dose adjustment for patients with mild and moderate hepatic impairment (APV10017) [abstract 1]. 8<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy. Budapest, Hungary, April 16-18, 2007.

Pérez-Elías M et al. Pharmacokinetics of fosamprenavir plus ritonavir in human immunodeficiency virus type 1-infected adult subjects with hepatic impairment. *Antimicrob Agents Chemother* 2009;53:5185-96.