

Selected Properties of Fosamprenavir

Other names	Telzir®, Lexiva® (US), GW433-908
Manufacturer	ViiV Healthcare ULC
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	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.
Effect of Food	Tablets: 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. Oral suspension: Adults: Take on an empty stomach. Administration of the fosamprenavir calcium oral suspension formulation with a high fat meal reduced plasma amprenavir AUC by approximately 28% and C _{max} by approximately 46% as compared to the fasted state. Pediatrics: take with food to aid palatability and adherence.
Protein Binding	~90% plasma protein bound (mainly AAG)

Vd	~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.
Tmax	1.5-4 hours (median 2.5 hours)
serum T ½	7.7 hours
Drug Concentrations	<p>Median steady-state plasma amprenavir pharmacokinetic values:</p> <ul style="list-style-type: none"> • 1400 mg BID dosing : Cmax 4.82 ug/mL, Cmin 0.35 ug/mL, AUC₂₄ 33 ug.h/mL • 1400 mg QD/ritonavir 200 mg QD dosing: Cmax 7.24 ug/mL, Cmin 1.45 ug/mL, AUC₂₄ 69.4 ug.h/mL • 700 mg BID/ritonavir 100 mg BID dosing: Cmax 6.08 ug/mL, Cmin 2.12 ug/mL, AUC₂₄ 79.2 ug.h/mL <p>In a retrospective analysis of 15 HIV/HCV coinfecting patients without cirrhosis receiving fosamprenavir 1400 mg BID, mean amprenavir AUC₁₂ was 35.3 mg.h/L, mean Ctrough 1.2 mg/L.[Barbarini G et al. 2009]</p>
Minimum target trough concentrations (for wildtype virus)	0.4 mg/mL (unboosted amprenavir)
CSF (% of serum)	<p>CSF/Plasma ratio: 0.45 – 1.30% (3 patients) (amprenavir)</p> <p>In 43 HIV-infected subjects on fosamprenavir regimens with matched CSF & 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 >IC₅₀wt (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>
Metabolism	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).
Excretion	Primarily hepatic metabolized. Excretion via biliary route.
Dosing – Adult	<p>PI-Naïve subjects:</p> <ul style="list-style-type: none"> • 700 mg/100 mg ritonavir po BID • 1400 mg/200 mg ritonavir po QD • 1400 mg/100 mg ritonavir po QD (US monograph) • 1400 mg BID (U.S. monograph only) <p>PI-Experienced subjects:</p>

<p>Dosing – Pediatric</p>	<ul style="list-style-type: none"> • 700 mg/100 mg ritonavir po BID <p>Canadian monograph information: Children (< 12 years of age) and Adolescents (12 to 18 years of age): The safety and efficacy of TELZIR® in combination with ritonavir have not yet been established in these patient populations.</p> <p>American monograph information: Pediatric Patients (≥4 weeks to 18 years of age): The dosage of Lexiva should be calculated based on body weight (kg) and not exceed the recommended adult dose.</p> <p>Twice daily dosage regimens by weight with ritonavir are as follows:</p> <ul style="list-style-type: none"> • for protease inhibitor-naïve pediatric patients (≥4 weeks of age) and • for protease inhibitor-experienced pediatric patients ≥6 months of age. (Lexiva plus ritonavir is not recommended for protease inhibitor experienced pediatric patients less than 6 month of age.) <table border="1" data-bbox="669 856 1432 1024"> <thead> <tr> <th>Body weight</th> <th>BID Dosing</th> </tr> </thead> <tbody> <tr> <td><11 kg:</td> <td>Lexiva 45 mg/kg plus ritonavir 7 mg/kg</td> </tr> <tr> <td>11 kg to <15 kg:</td> <td>Lexiva 30 mg/kg plus ritonavir 3 mg/kg</td> </tr> <tr> <td>15 kg to <20 kg:</td> <td>Lexiva 23 mg/kg plus ritonavir 3 mg/kg</td> </tr> <tr> <td>≥20 kg:</td> <td>Lexiva 18 mg/kg plus ritonavir 3 mg/kg</td> </tr> </tbody> </table>	Body weight	BID Dosing	<11 kg:	Lexiva 45 mg/kg plus ritonavir 7 mg/kg	11 kg to <15 kg:	Lexiva 30 mg/kg plus ritonavir 3 mg/kg	15 kg to <20 kg:	Lexiva 23 mg/kg plus ritonavir 3 mg/kg	≥20 kg:	Lexiva 18 mg/kg plus ritonavir 3 mg/kg
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<p>Special instructions for pediatric patients</p>	<p>Pediatric patients should take the suspension <u>with</u> food to aid with palatability and adherence.</p> <p>Fosamprenavir should only be administered to infants born at 38 weeks gestation or greater and who have attained a post-natal age of 28 days.</p> <p>Alternatively, protease inhibitor naïve children 2 years of age and older can be administered Lexiva (without ritonavir) 30 mg/kg twice daily.</p> <p><i>American monograph information:</i></p> <p>For pediatric patients, pharmacokinetic and clinical data:</p> <ul style="list-style-type: none"> • do not support once-daily dosing of LEXIVA alone or in combination with ritonavir • do not support administration of LEXIVA alone or in combination with ritonavir for protease inhibitor-experienced children younger than 6 months of age • do not support twice-daily dosing of LEXIVA without ritonavir in pediatric patients younger than 2 years of age 										
<p>Adjust in Liver Dysfunction</p>	<p>The following dose reductions are recommended: <u>Mild Hepatic Impairment</u> (Child-Pugh score ranging from 5 to 6):</p>										

	<p>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>Moderate Hepatic Impairment (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>Severe Hepatic Impairment (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 mild hepatic impairment, fosamprenavir 700 mg BID plus ritonavir 100 mg QD resulted in 17% ↑ C_{max}, 22% ↑ AUC, similar C_{tau} of amprenavir compared to subjects with normal hepatic function. In subjects with moderate hepatic impairment, fosamprenavir 300 mg BID plus ritonavir 100 mg QD yielded 27% ↓ C_{max} and AUC, 57% ↓ C_{tau} of amprenavir. In subjects with severe hepatic impairment, fosamprenavir 300 mg BID plus ritonavir 100 mg QD yielded 19% ↓ C_{max}, 23% ↓ AUC, 38% ↓ C_{tau} 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>
Adjust in Renal Failure/Dialysis	Dosage adjustment not required.
Toxicity	<p>rash 19% (SJS < 1%), diarrhea, nausea, vomiting, headache, 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>
Pregnancy & Lactation	<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 < 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>
Drug Interactions	Amprenavir is an inhibitor of CYP3A4. See separate Drug Interaction Table.
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	700 mg pink film-coated tablets, DIN 02261545; 50 mg/mL grape bubblegum and peppermint flavoured oral suspension, 225 mL bottle, DIN 02261553.
Storage	Bottles of 60 tablets. Store at room temperature in tightly sealed container. Store oral suspension between 2-30°C. Do not freeze. Discard the suspension 28 days after first opening.

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]. 10th International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 15-17, 2009.

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